VOLUME 60 • JULY 1958 • NUMBER 1

OPHTHALMOLOGY

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The Scleral Buckling Procedures
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The Sources of Fibroblasts in Corneal Wound Repair
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Radiography of Aqueous Humor Outflow
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Correspondence

College of Physicians of Philadelphia, Section on Ophthalmology

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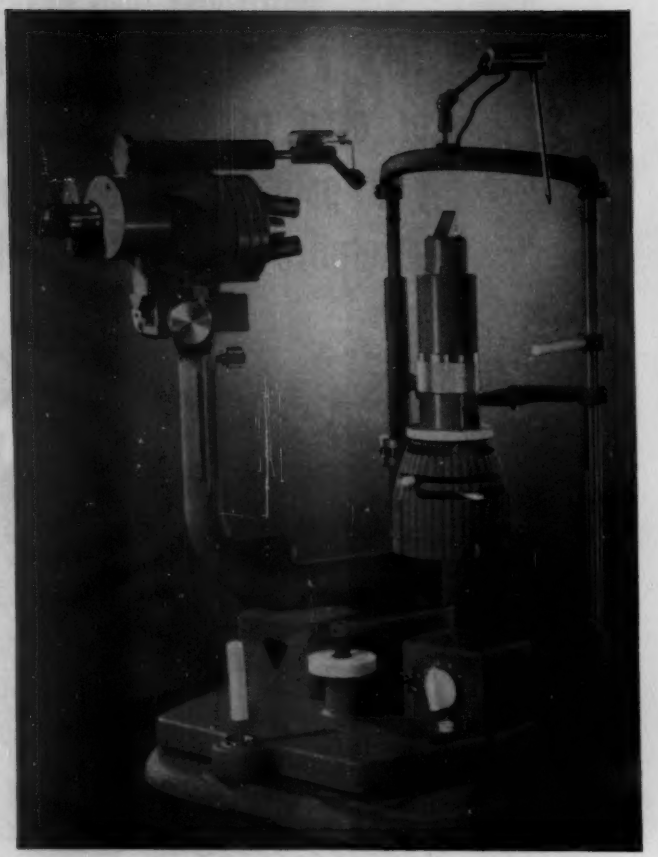

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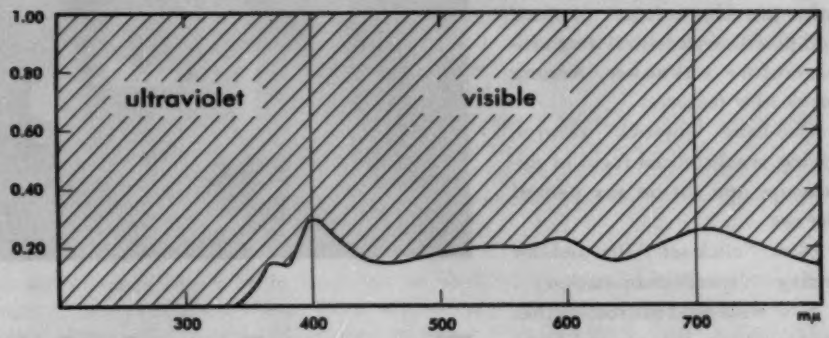

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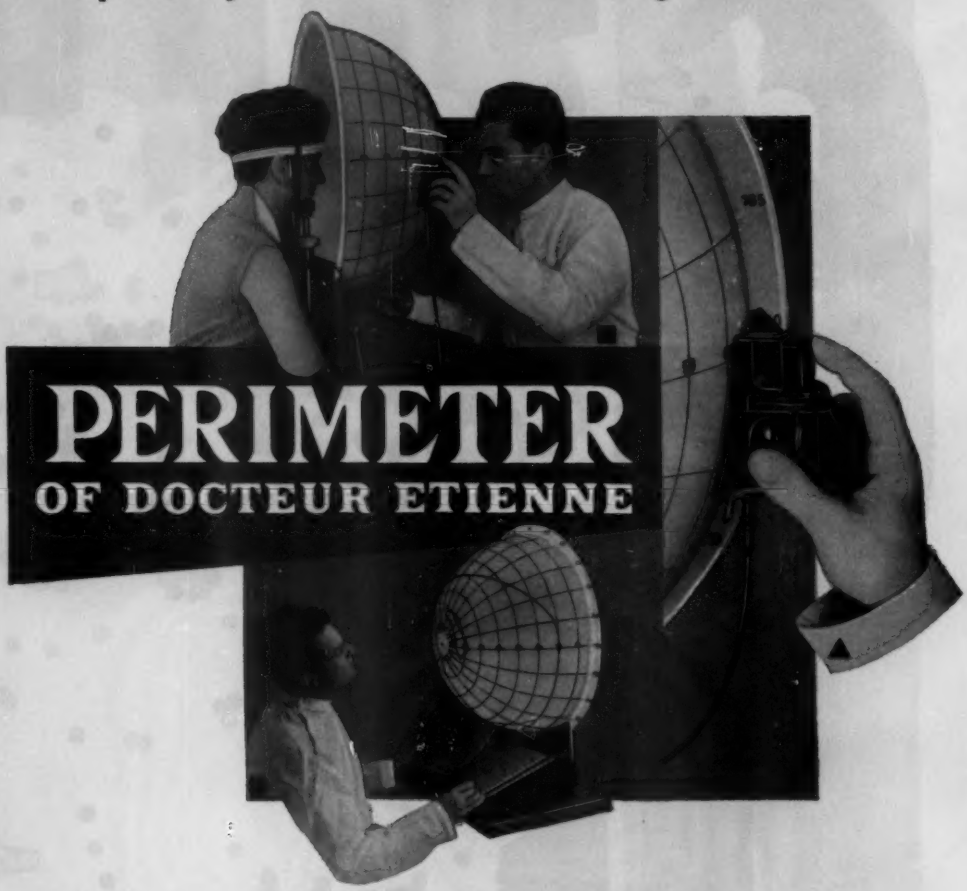

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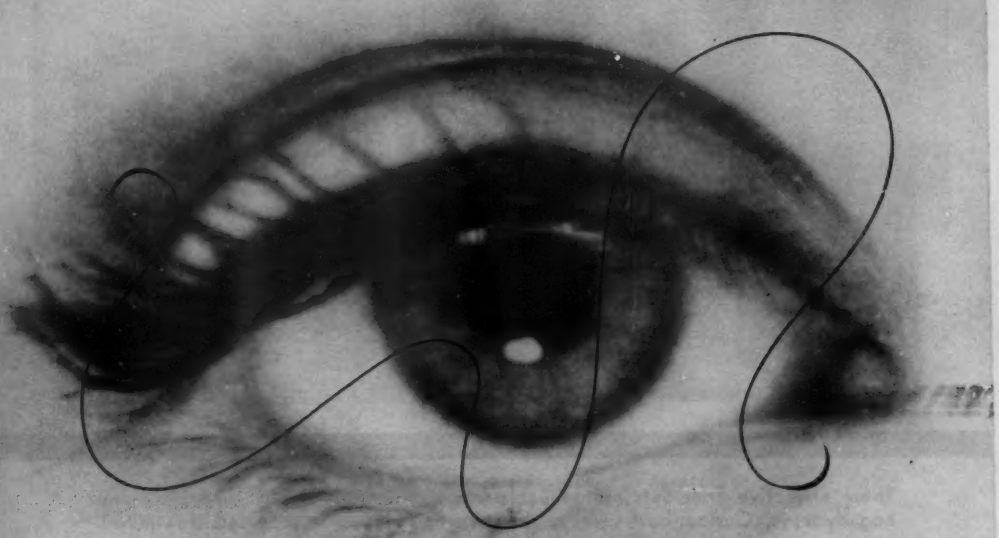

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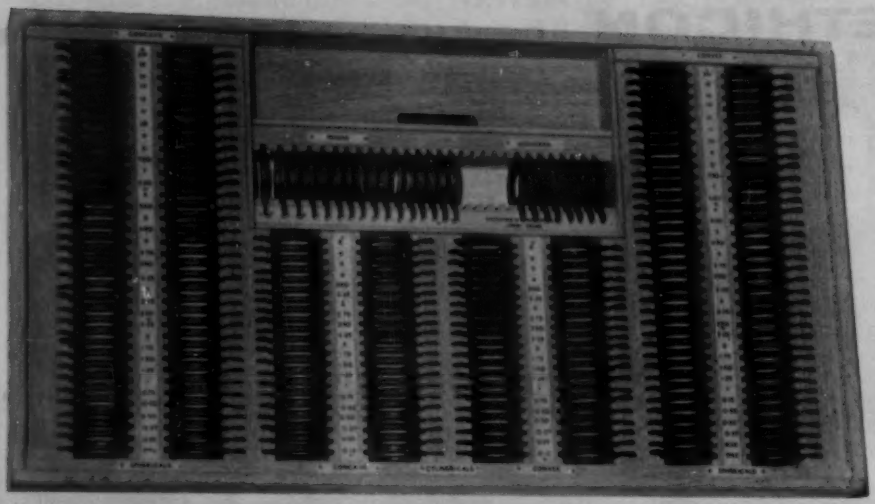

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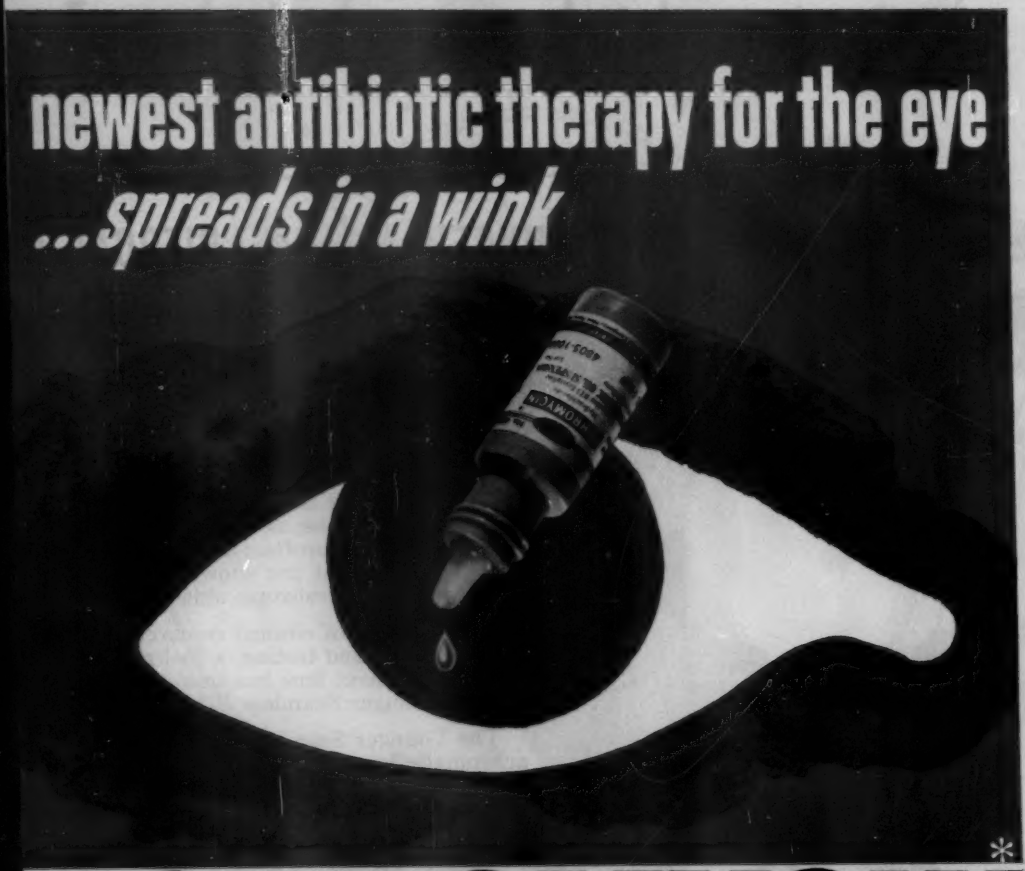

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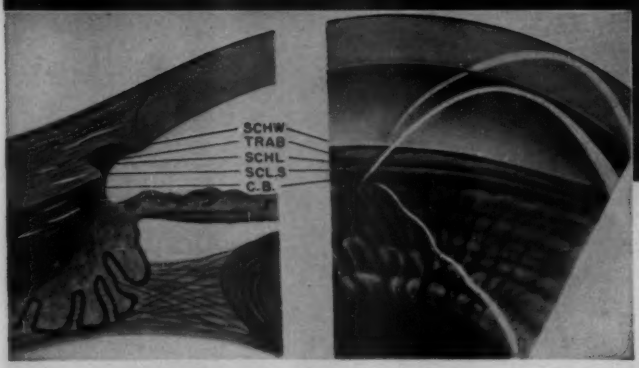

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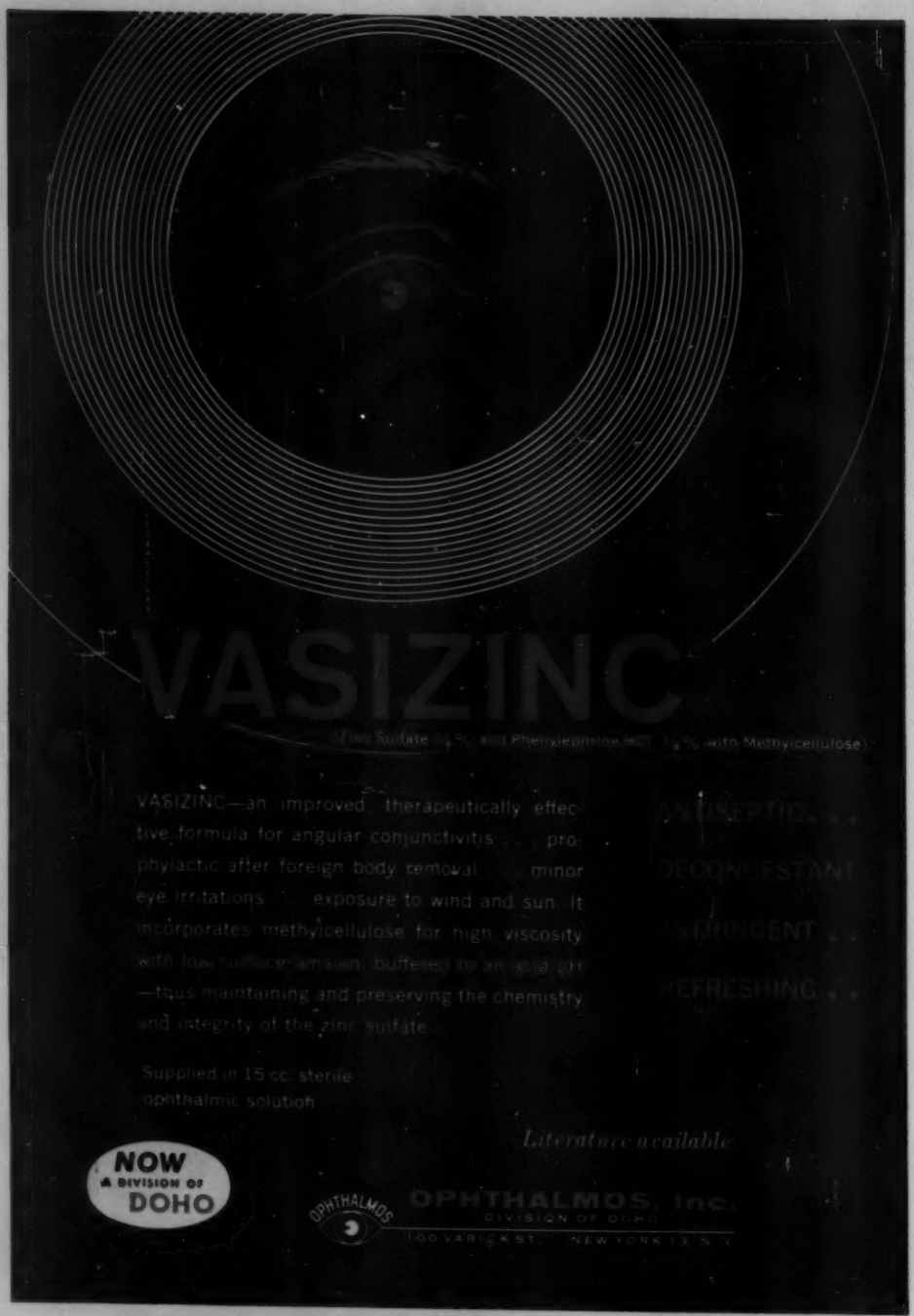
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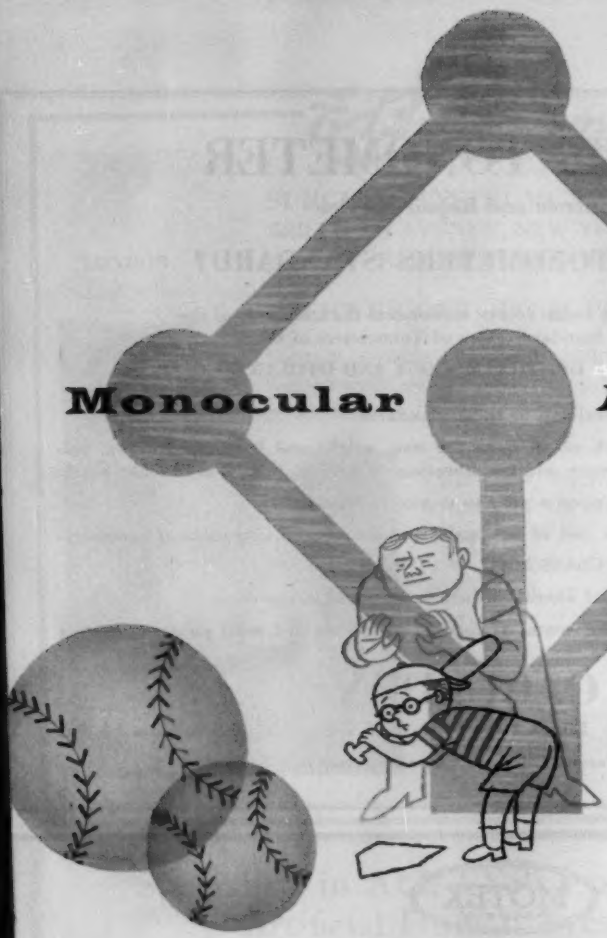

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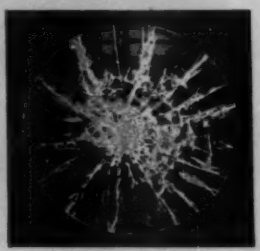

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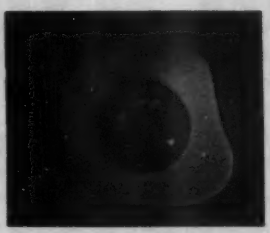

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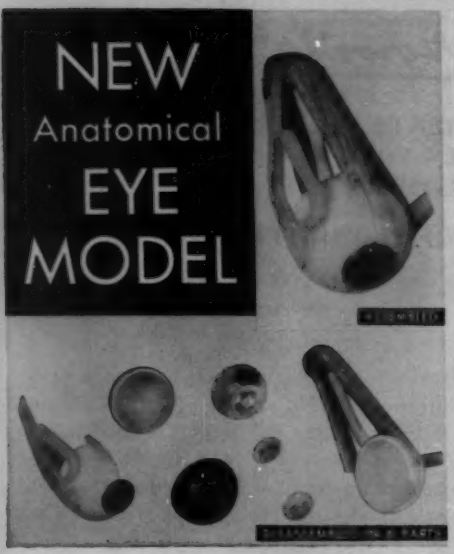

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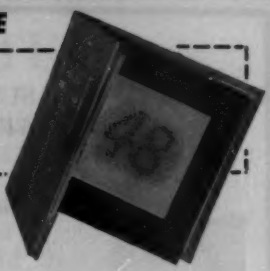

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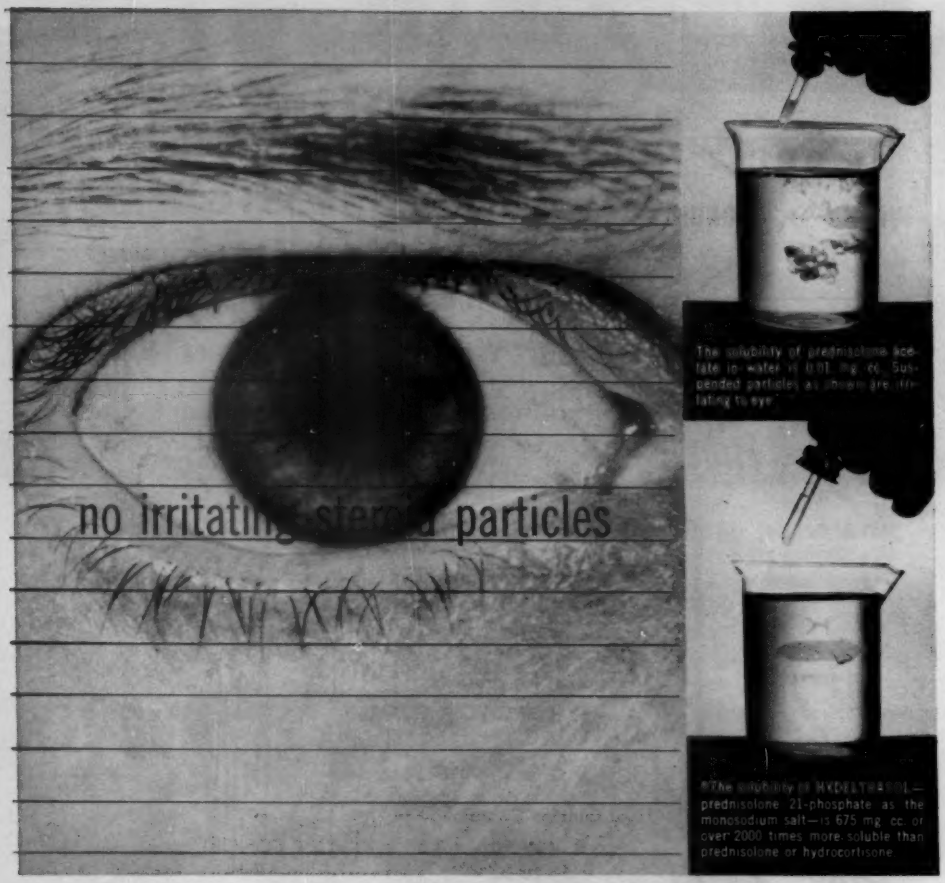
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Effect of Fungistatic Agents on Corneal Infections with Candida Albicans

JEROME A. MONTANA, M.D., and THEODORE W. SERY, Ph.D., Philadelphia

Introduction

Nystatin,* derived from an Actinomyces species, Streptomyces noursei, and amphotericin B,† derived from S. noursei sp. are two of a new group of fungistatic agents [1,2] which have been found to be effective against fungal infections. Chemically they have been shown to be conjugated polyene chromophores typified by nystatin, in which present knowledge indicates the structure to be a large molecule composed of (*a*) a 40-carbon unit containing polyene bonds, a carboxyl group, a lactone group, and 11 hydroxyl groupings and (*b*) a glycosidically bound 6-carbon amino sugar unit.[3] They have been shown to have very little antibacterial action [4] but in vitro show a wide range of antifungal activity, especially against the yeasts or yeast-like fungi.[1,5] These antibiotics are water insoluble and are stable when kept dry, cold, and in the dark but lose activity rapidly when in solution. Nystatin has been used widely in the treatment of monilial infections. It is used as an oral preparation or locally, with the intravenous or intramuscular route reserved if these fail. A water-soluble form of amphotericin B has been used intravenously with no severe toxic reactions.[6]

In the past years, there has been an increase in the number of fungus infections seen concomitantly with the increased use of corticoids and antibiotics.[7,8] Seligman [9,10] showed an apparent enhancement of the virulence of Candida albicans in mice when it was injected intraperitoneally along with oxytetracycline or cortisone. Intercurrent fungal infections are now a frequent and often serious complication of therapy with antibiotics and corticoids. This phenomenon has also been noted in ophthalmologic conditions. Mitsui and Hanabusa,[12] Ley and Saunders,[11] and others [13-15] have reported cases of fungus keratitis complicating treatment of corneal lesions with cortisone and broad-spectrum antibiotics. Experimentally, Ley [16] has shown that rabbits given cortisone subconjunctivally had a much higher infection rate when the cornea was given inoculations of various fungi, including C. albicans and Aspergillus terreus. C. albicans infection rates were also increased when oxytetracycline was used.

Because of the increasing probability that fungal infections may complicate various ophthalmologic conditions, newer antifungal agents merit consideration for their possible

Submitted for publication Nov. 5, 1957.

From the Research Department of the Wills Eye Hospital.

This investigation was supported in part by a research grant (2B-5076C2) from the National Institute of Neurological Diseases and Blindness, of the National Institutes of Health, Public Health Service, and from The Squibb Institute for Medical Research, New Brunswick, N. J.

* Nystatin is the generic name for Mycostatin of E. R. Squibb & Sons, New York.

† Amphotericin B is the generic name for Fungizone of E. R. Squibb & Sons, New York.

prophylactic and therapeutic effects. The purpose of this paper is to determine the ocular toxicity, penetration of the ocular tissues, and therapeutic possibilities of nystatin and amphotericin B in experimental corneal infections of rabbits with C. albicans.

Methods

Solutions of nystatin and amphotericin B for penetration studies and therapeutic application were dissolved in different ways. Nystatin was prepared in an ointment form by dissolving the sterile powder in propylene glycol and adding this to an ointment base. This was instilled in the lower conjunctival cul-de-sac and directly onto the cornea. Nystatin was also used in suspension in physiological saline. Amphotericin B, which was water-soluble, was dissolved in 5% glucose and used locally, subconjunctivally, and intravenously.

Intraocular penetration and tolerance of nystatin and amphotericin B in the rabbit were investigated for three modes of administration: (*a*) topical application to normal unabraded and mechanically abraded corneas of both ointment and instilled drops, (*b*) subconjunctival injections, and (*c*) intravenous injections (amphortericin B only). Albino rabbits of average weight (2.5 kg.) were used in all experiments. After local application of the drug, and just prior to aspiration of aqueous humor, the eye was washed with sterile saline, after which 0.5% sterile tetracaine (Pontocaine) was instilled into the lower conjunctival cul-de-sac. The aqueous humor was aspirated by use of a tuberculin syringe (wetted with heparin, 10 U. S. P. units per milliliter) fitted with a 27-gauge needle. For topical application 8 drops of the drug suspension or solution were instilled every 5 minutes into the lower cul-de-sac for 30 minutes. The aqueous humor was assayed for the drugs by the serial dilution technique, according to the same procedure that was used previously,[17] with the following modifications: (*a*) A strain of C. albicans‡ was the organism employed for antibiotic assay; (*b*) fresh cultures on Mycophyll agar (Difco) were used daily to prepare saline suspensions for inoculation into Sabouraud's broth; (*c*) twofold dilutions from 1:10 to 1:80 of aqueous in broth were made so as to give 1 ml. amounts of broth per tube; (*d*) inoculum per tube was roughly 3×10^6 viable cells in 0.05 ml.

Intracorneal injections of different agents were made with a sterile 27-gauge needle and tuberculin syringe. Animals were given general anesthesia with pentobarbital intravenously and tetracaine locally to facilitate this procedure.

Animals were examined daily for signs of infection with use of local application of sterile solutions of fluorescein and methylene blue (1%). All ocular lesions which developed were checked for C. albicans either by direct smear or culture of corneal scrapings on Mycophyll agar plates. Sections of several eyes were made to show the location of the infections.

Results

Toxicity.—When nystatin was used subconjunctivally (saline suspension) in amounts of 2000 units and greater there was local inflammation followed after several days by necrosis; a dosage of 800 units caused only a transitory conjunctivitis. Instilled drops could be used in concentrations of 100,000 units per milliliter without reaction. Amphotericin B caused no local tissue reaction when given subconjunctivally or as instilled drops in concentrations of 5 mg. per milliliter. It caused no apparent systemic reactions when 1 ml. doses of a solution containing 5 mg. of amphotericin B were given intravenously. These intravenous injections were always given slowly, usually over a period of five minutes; otherwise, an occasional death would result.

Ocular Penetration of the Antibiotics.—Penetration of nystatin into the aqueous

‡ Obtained from an active case of moniliasis at the Children's Hospital, Philadelphia.

Figure 1

Figure 2

Figure 3

Figure 4A

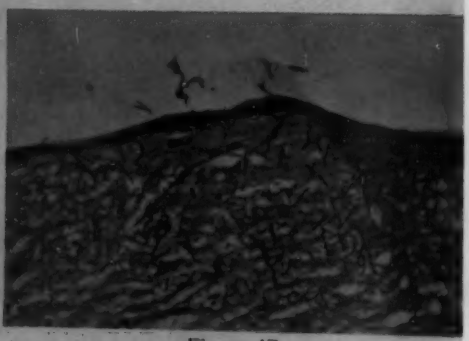

Figure 4B

Figure 5A

Figure 5B

was studied by giving it locally or subconjunctivally. Subconjunctival injections consisted of 0.2 ml. of a preparation containing 4000 U. per milliliter in saline. In like manner, amphotericin B was used in a concentration of 5 mg. per milliliter in 5% glucose and was given subconjunctivally, locally, or intravenously.

For local application both mechanically abraded and unabraded corneas were treated. Aqueous humor samples taken at 1, 2, 6, and 24-hour periods were assayed for the drug, as previously described. All these bioassays involving aqueous humor showed no detectable amounts of antibiotic in the aqueous under the experimental conditions described. Control tests with the broth-dilution technique gave growth inhibition, of the strain of C. albicans used,§ in the region of 8 units of nystatin and 0.6μg. of amphotericin B per milliliter. Since the lowest dilution of aqueous which could be tested conveniently was 1:10, one can estimate that aqueous levels below, roughly, 80 units and 6μg. per milliliter for nystatin and amphotericin B, respectively, would not have been detected by this method.

Treatment of Experimental Infections.—For testing the effect of the antibiotics in vivo against corneal infections a standard procedure of infecting rabbit corneas was required. Intracorneal inoculation of 0.01 ml. of saline suspension containing 10^3, 10^4, and 10^5 viable cells of C. albicans was tested in several rabbits. Each cornea received 30μg. to 60μg. of prednisolone (in approximately 0.03 to 0.06 ml.) by intralamellar injection just prior to inoculation. After one week of observation it was found that the 10^5-cell dose was invariably infective to the cornea, causing ulceration and hypopyon by the fourth day and perforation by the seventh day. This dose of cells along with steroid conditioning of the cornea was therefore used to infect all rabbits for in vivo antibiotic tests. In the absence of steroid conditioning no infections occurred with the above inocula, nor was it possible to produce infections by instilling the cells on the abraded cornea.

TABLE I.—*Effect of Prednisolone on Corneal Infection*

Intracorneal Injections	Eyes Given Inoculation, No.	Eyes Infected, No.
C. albicans alone	4	0
C. albicans 1 hr. or less after prednisolone	10	10
C. albicans 24 hr. after prednisolone	4	4
C. albicans 1 wk. after prednisolone	2	2
C. albicans 2 wk. after prednisolone	2	2

Experiments with and without prednisolone are summarized in Table 1. Of four animals that were given intracorneal (intralamellar) inoculations of C. albicans without prior use of prednisolone, no infection ensued. If a 30μg. to 60μg. dose of a solution of prednisolone was given intracorneally followed by an intracorneal inoculation of C. albicans suspension, infection would occur. This effect of prednisolone enhancement of corneal infection was noted to last at least two weeks.

Corneal infection was evident at the end of 48 hours, first appearing as a small corneal ulceration. After 72 hours there was evidence of increasing ulceration and formation of a hypopyon (Fig. 1). Over the course of the next several days there was progressive hypopyon formation, with evidence of iris injection and edema and in-

§ Our strain of C. albicans was compared with another strain (A. T. C. C. 11651). This strain was inhibited in growth in the region of 5 units per milliliter for nystatin and 0.6μg. per milliliter for amphotericin B, according to the conditions of our assay procedure.

Fig. 1.—Eye of rabbit 96 hours after receiving intracorneal injections of prednisolone and C. albicans. Evidence of ulceration and hypopyon may be seen. The contralateral eye, which received only C. albicans, was normal.

Fig. 2.—Same eye as in Figure 1, 48 hours later, showing corneal perforation. The contralateral eye was still healthy.

Fig. 3.—Section through cornea of untreated eye 24 hours after inoculation with C. albicans. Note that Descemet's membrane is still intact. Periodic acid-Schiff stain.

Fig. 4.—A similar section through an untreated eye 48 hours after inoculation, showing C. albicans mycelia at Descemet's membrane. Some organisms have already penetrated into the anterior chamber.

Fig. 5.—A similar section through an infected cornea 72 hours after the inoculation. Note that Descemet's membrane has ruptured, permitting entry of cells into the anterior chamber.

creased intraocular tension. By the fifth day the untreated infections usually showed corneal perforation, and at the end of one week the lens was proptosed (Fig. 2). Sections of eyes taken at various stages showed destruction of the cornea by C. albicans in both the yeast-like and the mycelial phase. It was also possible to confirm the nature of the infection by culturing corneal scrapings on Mycophyll agar, with reisolation of C. albicans.

In all cases, both eyes were given inoculations but only one was treated, the untreated eye serving as a control for comparison. Untreated control eyes all followed the above-described course of infection. Treatment with the nystatin ointment was begun in several eyes immediately after inoculation, while in other eyes treatment was delayed (Table 2). The ointment (100,000 units/3 gm. of ointment base) was applied liberally three times a day. Eyes treated immediately after inoculation and within four hours after inoculation developed no infection. When treatment was delayed 24 hours, infection developed in 6 of 10 eyes treated. This took the form of corneal ulceration, which gradually cleared as treatment continued, leaving a corneal nebula. In all eyes where treatment was delayed for 48 hours or more, infection developed and progressed as in the untreated eyes.

Amphotericin B (5 mg. per milliliter in 5% glucose) was used in the treatment of the corneal infections by three routes. It was given by subconjunctival injections (0.3 ml.) once a day; instilled drops three times a day, or intravenously (1.0 ml.) once a day. Results of this experiment are summarized in Table 3. None of the eyes which were treated by subconjunctival injection were free of infection, including those where treatment was started immediately after inoculation. Eyes treated in this manner showed no appreciable difference from the untreated control eyes. When amphotericin B was administered as instilled drops, no infections developed in those eyes treated within the first 24 hours after inoculation. Eyes treated at 48 hours developed small ulcerations which yielded no growth of C. albicans on culture of scrapings. If treatment was delayed 72 hours or longer, there was no difference between treated and untreated control eyes. Similar results were obtained with use of amphotericin B intravenously. Animals treated intravenously within four hours of inoculation showed no evidence of infection. One week later the same eyes were given inoculations again and not treated, and C. albicans infections developed. Eyes treated at 24 and 48 hours after inoculation developed small ulcerations on the cornea, but these did not progress. When the drug was withheld for 72 hours, there was no difference between treated and untreated control eyes.

TABLE 2.—*Treatment of Corneal Infections with Nystatin Ointment*

Time Between Inoculation and Start of Treatment, Hr.	Eyes Treated, No.	Treated Eyes Developing Infection, No.	Degree of Infection
0	8	0	--
4	6	1	Mild
24	10	6	Mild
48	5	5	Severe
72 (or longer)	6	6	Severe

TABLE 3.—*Treatment of Corneal Infections with Amphotericin B*

Manner of Drug Administration	Time Between Inoculation and Start of Drug Treatment, Hr.	Eyes Given Inoculations & Treated, No.	Treated Eyes Developing Infection, No.	Degree of Infection
Instilled drops	0	2	0	--
	4	2	0	--
	24	2	0	--
	48	2	1	Mild
	72	2	2	Severe
Intravenous	0	2	0	--
	4	2	0	--
	24	2	2	Mild
	48	2	2	Mild
	72	2	2	Severe
Subconjunctival	0	3	3	Severe
	4	2	1	Severe
	24	2	2	Severe
	48	2	2	Severe
	72	4	4	Severe

Comment

Both nystatin and amphotericin B would appear to have little or no therapeutic value when used in the treatment of an established infection of the rabbit cornea with C. albi-

cans. The above results indicate the probability that these drugs are able to prevent infection with C. albicans when given during the latent period or very early in the course of infection. Sections taken during the course of an untreated infection show that by the end of 24 hours Descemet's membrane was still intact (Fig. 3). After 48 hours active penetration of this membrane by the mycelial elements had become evident (Fig. 4), and by the end of 72 hours Descemet's membrane had ruptured (Fig. 5), leading to an eventual intraocular infection and death. It would seem probable that once the infection is established the infectious process is unable to be altered by these drugs. Although the experimental method did not rule out the presence of antibiotics in the aqueous below previously described levels, it would appear that they could not have been present in sufficient levels or in forms utilizable to inhibit an established infection. Furthermore, the prevention of infections of the cornea with nystatin within the first 24 hours and with amphotericin B within the first 48 hours suggests an intracorneal penetration by the drugs when they are administered either locally or (as for amphotericin B only) intravenously. The data suggest that amphotericin B is able to penetrate the corneal stroma from the limbal vessels as well as through the intact corneal epithelium. The failure of subconjunctival injection of antibiotics to alter the course of corneal infections implies that the conjunctival and scleral tissues offer a relatively impermeable barrier to these antibiotics or at least that penetration did not take place before the drug was removed from this depot for excretion.

Both antibiotics appeared to be innocuous in relatively high concentrations. Only nystatin presented toxic effects when 2000 units or more were given subconjunctivally. Amphotericin B, however, was not used above a concentration of 5000μg. per milliliter, and so toxic levels for the eye were not determined.

Ley [16] has shown the effect which cortisone produces in the cornea of experimental animals, increasing their susceptibility to various fungal infections; the exact nature of the mechanism by which cortisone exerts this effect is not understood. The related steroid compound, prednisolone, as might be expected, appears to have the same effect. The infections with C. albicans are much more easily established and run a more fulminating and extensive course when preceded by treatment with prednisolone. The long-term effect that has been observed here, in which steroid treatment enhances subsequent infections that are given weeks later, is an interesting sidelight and deserves further investigation.

The data suggest that these drugs act prophylactically and can prevent infection with C. albicans when it is first introduced at around 10^5-cell doses. These drugs are fungistatic rather than fungicidal and therefore depend also on tissue defenses in the cure of infection. In the light of the reports of increasing numbers of cases of fungus infections of the eye following the use of corticosteroids and broad-spectrum antibiotics, nystatin and amphotericin B may have clinical therapeutic as well as prophylactic applications.

Summary

Nystatin and amphotericin B, two of a new group of fungistatic antibiotics, were tested in rabbits to determine their ocular toxicity, ocular penetration, and therapeutic effect against Candida albicans infections of the cornea. Amphotericin B, at the concentration used, was nontoxic to ocular tissues when applied locally, subconjunctivally, and intravenously. Nystatin, however, was injurious when given subconjunctivally but not when given topically.

Neither drug penetrated into the aqueous humor, from those sites where they had been applied, in amounts detectable by the method used.

Positive inhibition of C. albicans infections of the cornea could be effected with

either drug if treated early enough and with the proper route of administration. Intracorneal injections of prednisolone, which was needed to produce suitable infections, could enhance infection of the cornea as late as two weeks after the steroid was administered.

The possible prophylactic action of these antibiotics is discussed.

Dr. Irving H. Leopold suggested the problem of this study and gave encouragement and interest; Dr. Gavin Hildick-Smith, M. R. C. P., of The Squibb Institute for Medical Research, gave information from his own investigational work; Mrs. Maria Patti Notaro, H.T., did all the histological work, and Mr. Paul Weaver, M.S., of Children's Hospital, Philadelphia, provided a strain of C. albicans isolated by him.

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Some Observations on Divergence Excess

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Many excellent papers [1-9] have been written recently concerning the type and amount of surgery to be done for the more perfect correction of intermittent exotropia. To satisfy my own curiosity and to add further clarity to this field, I reviewed 451 consecutive cases of exotropia done on the ward service of the Massachusetts Eye and Ear Infirmary. These included: (1) overcorrected esotropias, (2) constant exotropias, (3) alternating exotropias, (4) exotropias which have as their basis reduced vision and resultant deviation, and (5) intermittent exotropias with (*a*) convergence insufficiency and (*b*) divergence excess.

Only in this last category was it possible to find any definite relationship between type and amount of surgery and the degree of stereopsis.

Method of Selection of Cases

In Category 5, intermittent exotropia, I have used Costenbader's classification [3] for delineating divergence excess, and only this will be covered in this paper. The characteristics for divergence excess exotropia are (1) exophoria or exotropia for distance and binocular alignment for near within normal limits, (2) intermittence, (3) near point of convergence and prism convergence good.

For the sake of continuity in pre- and postoperative management, as the residents at the Massachusetts Eye and Ear Infirmary change service every three months, only cases that are or have been under surveillance by the orthoptic clinic are being utilized. Some of these persons have had home exercise, but none have had exercises on the major amblyoscope.

The near recording, on analysis of the data, shows greater correlation than that for distance alone or in combination with the near. The cases were further subdivided into those with 25△ of exophoria or less at near and those having greater than this amount.

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Surgical Techniques Employed

When one reads over the surgical notes, great similarily of technique is apparent, although very seldom did the same resident surgeon perform more than one surgical procedure. No case record is used where the operative record cast doubt on the smoothness of the procedure.

The standard operations are as follows: Incision is made through conjunctiva usually in front of, or above and below, the insertion of the muscle on the globe. If tenotomy is employed, first a hemostat is applied across the whole belly of the muscle and then, upon removal, incision is executed in the preformed hemostat trough. Recessions entail, after insertion of a double-armed 0000 mild chromic absorbable surgical (gut) suture through the tendon, locking it at either end, and then severing it from the globe, a most careful freeing of all attachments to the muscle sheath, so that the muscle snaps back into the orbit. The sutures are then inserted in the sclera at the desired length from the muscle stump and then tied, either as they are or after being brought up through the stump of the muscle. In resection, at the Massachusetts Eye and Ear Infirmary, there is no freeing up of the lateral bands. Two double-armed 0000 chromic gut sutures are inserted into the muscle at the desired length, tied, and then brought up through the stump. The excess muscle is then removed.

Grading of Results

(*a*) Poor, when the pupillary axes were either widely divergent or convergent, so that the eyes were not cosmetically straight

(*b*) Cosmetic

(*c*) Fusing Worth four dots, distance and near

(*d*) Binocular.

For the criteria of binocularity, I have used Cooper's classification,[2] slightly amended, which is as follows: (1) fusion during everyday existence; (2) bar reading; (3) fusing Worth four-dot test, distance and near; (4) no demonstrable tropia on doing a cover or uncover test; (5) no incomitance.

Results

I. There were 36 bilateral recti recessions. Twenty of these had 25△ of exophoria or less at near, with the following over-all results:

	Cases	
	%	No.
1. Binocular	70	14
2. Worth four-dot	15	3
3. Cosmetic	10	2
4. Poor	5	1

(*a*) In those seven cases in which a 6 mm. or greater recession was done, the results were as follows:

	Cases	
	%	No.
Binocular	85.7	6
Worth four-dot	14.3	1

(*b*) In the eight cases that had 5 mm. bilateral recessions the results were as follows:

	Cases	
	%	No.
Binocular	75	6
Cosmetic	25	2

(*c*) In the five cases that had 4 mm. or less bilateral recessions the results were as follows:

	Cases	
	%	No.
Binocular	40	2
Worth four-dot	40	2
Poor	20	1

II. The remaining 16 cases in this group, i. e., those with greater than 25△ of exophoria had the following over-all results:

	Cases	
	%	No.
Binocular	25	4
Worth four-dot	18.7	3
Cosmetic	37.5	6
Poor	18.7	3

(*a*) Those with 7 mm. or greater bilateral recession had the following results:

	Cases	
	%	No.
Binocular	28.6	2
Worth four-dot	14.2	1
Cosmetic	28.6	2
Poor	28.6	2, with moderate myopia

There were two reoperations in this group, one of which ended with a poor result and one with fusing the Worth four dots, both patients being moderate myopes, however.

(*b*) Those with 5 or 6 mm. bilateral recessions had the following results:

	Cases	
	%	No.
Binocular	22.2	2
Worth four-dot	22.3	2
Cosmetic	44.4	4
Poor	11.1	1

The one reoperation in this group ended in binocularity.

The results of performing tenotomies on the lateral recti are as expected—great variability. Four of these cases would have done well with recessions alone, i. e., those with 25△ of exophoria or less at near.

The results were as follows:

	Cases	
	%	No.
Binocular	50	2, with 1 reoperation
Worth four-dot	25	1
Poor	25	1, with 25△ of esotropia

The one that was a so-called unfavorable case also had a poor cosmetic result, but it was exotropic.

The six recession-resection cases demonstrate the relative merits of symmetrical surgery. Five of these are considered favorable cases (25△ or less).

	Cases	
	%	No.
Binocular	60	3; 2 could not bar read
Cosmetic	40	2

One in each of the above categories required reoperation. The one so-called unfavorable case was truly unfavorable, ending with a poor surgical result.

The three bilateral medial recti resections are also disappointing. Those two that I consider as favorable had the following results:

	Cases	
	%	No.
Binocular	50	1, after reoperation
Cosmetic	50	1

That case which is considered unfavorable with one operation ended in a cosmetic result.

Both unilateral rectus recessions are disappointing, in that in one the result was only binocular after two operations and the other only achieved a cosmetic result.

Those eight cases in which a vertical muscle inbalance is present show the following results: All four cases with less than 25△ were binocular, but only one had oblique surgery and this was bilateral inferior oblique myectomy. This was the case that also had bilateral lateral rectus tenotomy. In the four cases that were unfavorable the result was binocular in 25% (1 case, inferior oblique myectomy O. U.), cosmetic in 25% (1 case), and poor in 50% (2 cases, one of which was a high myope).

Comment

When a youngster or adolescent or even an adult confronts the ophthalmologist with a divergence excess exotropia, which muscle should be attacked and what type of surgery

Summary of Cases

Amt. Dist	Squint Near	Muscle Aberration	Age Yr.	Operations Amt.,, Mm.	Type	Result	Prescription
					Tenotomy		
40	25	10 over	8	8	Recession IO	Binoc (1)	
35	25		12		Tenotomy LLR		
				7	Resect LMR		
			20	3.5	Advance RMR		125
				5	Recession RLR	Binoc (2)	150×180
25	15		8		LROU	Poor (25 ET)	500—350×10
							350—200×175
35	25		23		LROS	WL D&N	25
							175—125×175
50	40		8		LROU	Poor (25 XT)	200
					Recession Resection		
36	25		5	5	Recess LLR		
				3	Resect RMR		
			7	6	Resect LMR		
				8	Recess RLR	Cosmetic	250—100×180
16	2		8	6	Recess LLR		
				3	Resect LMR	*Binoc	100
							350
25	14		12	4	Resect LMR		
				7	Recess LLR	*Binoc	
50	18	Nystagmus	11	7	Recess RLR		150
				3	Resect RMR	Cosmetic (2)	200
60	20		15	8	Resect LMR		
				8	Recess LLR		
			15	6	Recess RLR		—75—50×10
				8	Resect RMR	Binoc (½)	—25—50×170
60	50	12 LHT	28	6	Resect LMR		
				6	Recess LLR	Poor (XT)	
					Resection Medial Recti		
50	20		12	6	MROU		
			13	3	Resect RMR		
				5	Recess RLR	Cosmetic	
60	30		21	8			—350
			21	7	Recess LROU	Binoc (2)	—200
35	35		8	5		Cosmetic	150—150×180
							125—150×180
					Recession of One Lateral Rectus		
18	18		11	7	RLR	Cosmetic	100—100×30
							125—100×165
25	6	LIO over	7	6	LLR		
			10	7	Recess RLR	Binoc (½)	275
							350
					Recession of Lateral Rectus O. U. and One Medial Rectus		
50	45		19	5	LROU		
				5	LMR	Cosmetic	

* No bar reading.

should one do? A recession-resection? One lateral and if necessary the other? A tenotomy or bilateral rectus recessions? These problems as yet have no exact answer. However, the excellent work on electrical potentials observed during convergence and divergence[10,11] would seem to add strength to the theory that divergence is an active phenomenon. Since this is the case, theoretically, attack on the lateral recti is indicated. Certainly on reviewing the presentation of these data, one can see that bilateral recessions of even tremendous amounts (10 mm.) did not result in esotropia. One can also say that in this category are the greatest number of binocular patients, both numerically and statistically. However, this is an extremely small series.

Tenotomies, when performed on the lateral recti, had great variability and unpredictability of results—one even ending in that unsought-for position, esotropia.

Initial attack on the medial recti, except where there is a very large exotropia, and in conjunction with bilateral lateral rectus recessions, would not seem to be indicated by those who adhere to the theory of divergence as an active impulse. I think the data substantiate this.

Recession-resections, while producing good cosmetic results, give incomitance and a lower percentage of binocularity. With this is a higher incidence of reoperation (40% being reoperated on). It would seem that good results are not obtained until both laterals are recessed. This is true also when one lateral rectus is operated on. The one good result was not obtained until the other rectus had been recessed.

When the vertical deviations are placed in their proper perspective, they do not seem to impair the good results if proper horizontal surgical procedure is utilized. In fact, they enjoy a very good prognosis. In the favorable cases, there was 100% binocularity.

Is there a direct correlation between degree of squint and amount of recession? As Scobee[4] and Townes[5] have pointed out, in the case of exophoria or small degrees of exotropia one should not perform small amounts of surgery, for most certainly the results leave much to be desired. I feel that 7 to 9 mm. of recession of both lateral recti, regardless of the amount of deviation, is in order as a primary procedure on all divergence excess exotropias. This series certainly points out that when one is dealing with this type of squint and a recession operation esotropia is not to be feared.

What are the important prognostic factors? Probably the most important in this series is the amount of myopia. There is only one case which is binocular that has myopia of greater than −1.00 D. All those with greater than this amount have ended with something less than binocularity. The next factor is the amount of deviation for near, and the third is the type and amount of surgery performed. Although age at operation did not seem as important in the final outcome as the other factors, it would seem reasonable to create alignment in these youngsters before they reach the age of intensive near work in schools and after the noncooperativeness of the first few years of life (6 to 9 years of age).

Summary

Fifty-four cases of divergence excess exotropia are reviewed, and the following points were apparent:

The deviation at near is the most important measurement.

Cases with 25△ of deviation or less at near had good surgical results.

Any patient with more than 1 D. of myopia had a poor prognosis.

Bilateral lateral rectus surgery gave the best results when the amount of surgery was greater than 6 mm.

Vertical muscle imbalance did not seem to affect the outcome when proper horizontal surgery was performed.

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Metastatic Carcinoma of the Retina

Report of a Case and the Pathologic Findings

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Metastatic carcinoma of the eye involving the retina alone is an extremely rare lesion; only two reports of previous cases have been found in a review of the literature. The first report was that by Arisawa[1] in 1914. However, Smoleroff and Agatston[3] reviewed this case, which was in Sattler's[2] textbook, and concluded that the tumor involved the optic disc as well as the retina. In their article they reported a case of secondary carcinoma limited only to the retina. Our report is of a secondary carcinoma of the macula of the right eye, the primary site of the tumor being the rectosigmoid.

Report of Case

A 51-year-old white man was first seen by one of us (W. D. R.) on Jan. 30, 1956, because of blurred vision of one month's duration in the right eye. The corrected vision in the right eye was limited to counting fingers at 2 ft.; the corrected vision in the left eye was 20/20. His corrected vision four months previously was 20/30 in each eye, at which time he had no significant ocular complaints. The results of the external examination were negative. The positive ophthalmoscopic findings were limited to the right eye, where there was a sharply circumscribed grayish-white lesion in the macula about ⅙ dd. in size. A minimal amount of edema surrounded the lesion, but no hemorrhages were noted. Examination with the Hruby lens revealed that the lesion extended slightly forward into the vitreous. A small vascular twig coursed over the nasal side of the lesion; the rest of the fundus was normal. Upon questioning, the patient stated that he had had intermittent rectal bleeding for which he had had a fistulectomy nine months previously. The patient was then referred to a proctologist, whose diagnosis was annular carcinoma of the rectosigmoid. The clinical impression was metastatic carcinoma to the choroid with macular involvement. He was seen in consultation at The Cleveland Clinic in the Department of Ophthalmology on Feb. 8, 1956. Figure 1 shows the appearance of the lesion of the fundus at that time.

On Feb. 19, 1956, the patient was admitted to Massillon City Hospital, Massillon, Ohio, where he underwent rectosig-

Fig. 1.—Photograph of the right fundus as it appeared four months prior to enucleation. The neoplasm is evident as a small pale patch in the macular region.

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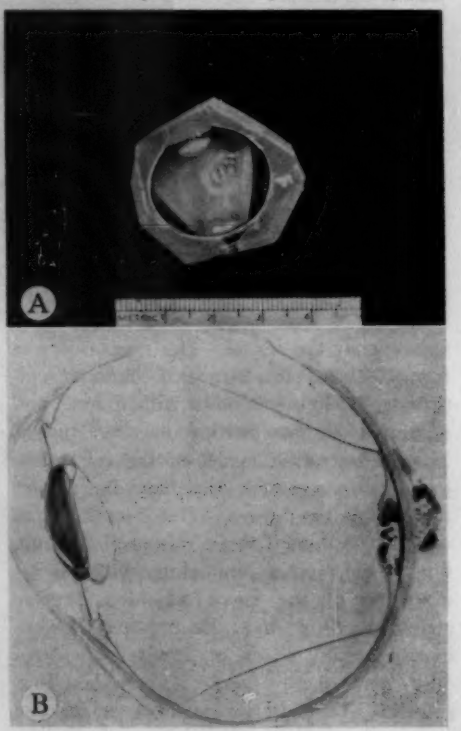
Fig. 2.—Photograph of the right fundus as it appeared one month prior to enucleation, showing marked enlargement of the lesion.

moidectomy. The pathologic diagnosis was adenocarcinoma of the rectosigmoid, Grade 3. A roentgenogram of the chest on Feb. 25, 1956, was reported as "negative." Ophthalmoscopic examination on May 29, 1956, revealed that the lesion in the macular region of the right eye had enlarged, with new vessels coursing over it (Fig. 2). Enucleation was advised and was accomplished on June 13, 1956. Sections of the eye revealed a neoplasm involving the retina and histopathologically similar to that found in the rectosigmoid. Further follow-up revealed no evidence of neoplasm in the orbit; however, in September, 1956, the patient went into coma and died, most likely because of generalized metastases. Permission for necropsy was not granted.

Pathologic Findings

The enucleated eye was fixed in 10% formalin and then was embedded in celloidin. Gross sections after embedding revealed a small discoid grayish-white nonpigmented lesion at the posterior pole, elevating the retina but not distending the choroid (Fig. 3*A*); the anterior segment was within normal limits, as were the sagittal sections that included the optic nerve. Serial sections for microscopic examination were taken temporally from a point just nasal to the medial margin of the lesion, until the lateral border of the lesion was passed. Every 10th section was stained, providing 30 slides for study. The sections adjoining the nasal border of the lesion showed a pink-staining acellular fluid elevating the retina from the retinal pigment layer. Temporal to this, the tumor mass was in the retina and in the adjoining subretinal space (Fig. 3*B*). The involved retina had lost its normal architecture, and there was necrosis and degeneration of the various layers (Fig. 4*A*). In some sections, clumps of dark-staining tumor cells were in the nerve-fiber layer, but there was no apparent localization of a tumor embolus in a vessel. The choroid was normal except for focal sites of lymphocytic perivascular infiltration and hyperemia in the region

Fig. 3.—Sections of the right eye through the neoplasm. *A*, gross appearance after the eye was embedded in celloidin, showing a small neoplasm in the posterior pole of the eye. *B*, photomicrograph of a section showing the tumor in the retina and subretinal space. Hematoxylin and eosin; ×4.



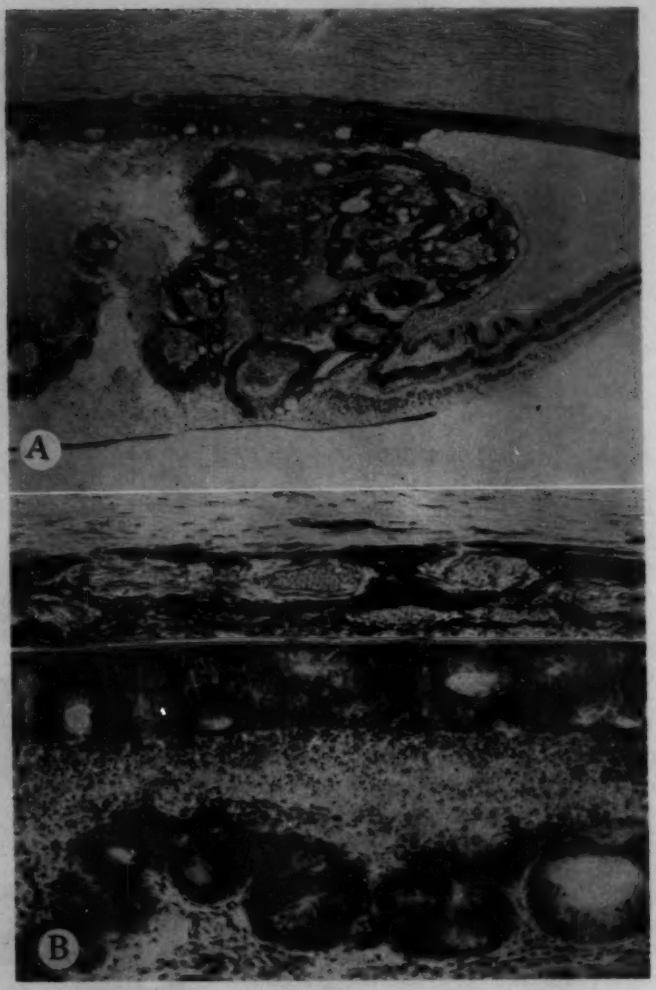


Fig. 4. — Photomicrographs of sections of the right eye. *A*, low-power view, showing the neoplasm in the retina and extending to the subretinal space. Dark-staining cells are gathered about lumens; necrosis of the retina and the tumor is evident. Neoplastic cells adjoin the lamina vitrea, which is intact. Hematoxylin and eosin; ×38. *B*, high-power view, showing atypical pseudostratified columnar cells, lumens, and necrosis. The choroid is hyperemic but free of tumor. Hematoxylin and eosin; ×185.

adjacent to the lesion. The neoplasm was formed of atypical stratified-columnar epithelial cells in small nests with lumens and separated by patches of necrotic tumor. The dark-staining nuclei of the cells were irregular in size and shape, and there were a few mitotic figures. The lamina vitrea was intact, though there was local destruction of the pigment epithelium where a flat extension of the tumor adjoined Bruch's membrane (Fig. 4*B*). No tumor cells were in the choroid, sclera, optic nerve, or vitreous, and there were no implantation growths. The anterior segment of the eye was normal. The microscopic evidence supported a diagnosis of adenocarcinoma of the retina, metastatic from the rectosigmoid.

Microscopic sections of the previously resected rectosigmoid were obtained from Dr. E. S. Kerr, Massillon, Ohio. These revealed a neoplasm similar to that observed in the retina (Fig. 5).

Comment

Arisawa's [1] case was that of a 30-year-old white man who had a carcinoma of the pancreas. Ophthalmoscopic examination re-

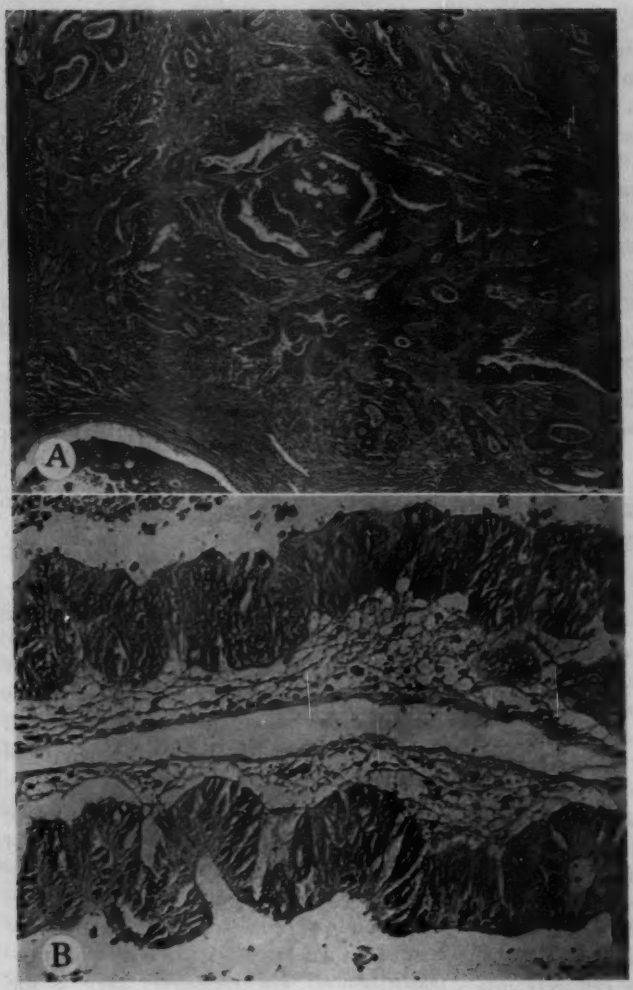


Fig. 5. — Photomicrograph of the adenocarcinoma of the rectosigmoid, showing characteristic lumen formation and fibrous stroma. *A*, low-power view. Hematoxylin and eosin; × 38. *B*, high-power view. Hematoxylin and eosin; × 180.

vealed a large mass projecting into the vitreous. Microscopic examination revealed a tumor that occupied two-thirds of the vitreous and that was connected with the head of the optic nerve by means of a pedicle. The greater part of the retina was replaced by neoplastic tissue. The tumor did not invade the choroid, and the pigmented epithelium was everywhere intact.

Smoleroff and Agatston's[3] case was that of a 55-year-old man who had an adenocarcinoma of the lower end of the esophagus and the cardiac end of the stomach. Ophthalmoscopic examination revealed an irregularly outlined large white mass in the inferior temporal quadrant of the right eye. The patient soon died, and the eye was removed at necropsy. Microscopic examination of the involved eye revealed a tumor that arose from the retina and grew in the subretinal space. It destroyed the pigmented epithelium but did not invade the lamina vitrea or the choroid. The implantation site of the tumor was in the nerve-fiber layer, where a small group of tumor cells appeared to originate from the wall of a blood vessel.

Since Perls [4] in 1871 described a bilateral metastatic carcinoma of the choroid, first of the left and then of the right eye, with the primary lesion in the right lung, there have been many reports of secondary carcinoma of the choroid, though it still is an infrequent lesion. There have been excellent reviews [5-10] of this subject. No additional cases of metastatic carcinoma limited to the retina were mentioned in these reports, nor were any others found in a review of the literature.

In regard to metastatic carcinoma of the choroid, the breast is the most frequent primary site of carcinoma in females and the lung, in males. The intestinal tract infrequently is a source of secondary choroidal carcinoma, accounting for only about 7% of all cases. In contrast, the retinal metastasis in our case and in the previous two reports [1,3] originated in the gastrointestinal tract or in the pancreas.

It is interesting to speculate on the mode of dissemination of this tumor to the eye. McCormack, Hazard, Turnbull, and Belovich [11] reported the presence of tumor cells in the venous drainage of malignant neoplasms. Venous blood was withdrawn from resected carcinomas of the colon-rectum, lung, and kidney; was subjected to centrifugation, and was stained for tumor cells. Tumor cells were identified in 12 of 50 cases of colorectal, 3 of 5 cases of pulmonary, and in both of 2 cases of renal-cell carcinoma. Once the tumor cell gets into the venous blood, its fate is said to depend not upon the variation in the susceptibility of different organs to the growth of secondary tumors but upon the availability of the tumor cell as an embolus.[12] Thus, the frequency of metastasis to the various organs is correlated positively with the number of embolic tumor cells that reach the capillary bed and not with the local "soil" factors. Reese [13] stated that the high incidence of carcinoma of the breast as the primary focus in metastatic carcinoma to the choroid is due to the rugged character of this type of cancer cells, with a consequent greater ability to survive and propagate under circumstances unfavorable to other cancer cells.

Batson [14] demonstrated that the vertebral vein complex can act as a bypass for other venous systems or as a venous pool. This is a separate venous system, and with increased abdominal pressure the venous flow from the pelvic veins is to the vertebral veins. Coman and DeLong [15] showed that tumor cells injected into the femoral veins of experimental animals, while abdominal pressure was applied, resulted in the appearance of these cells in the vertebral venous system in 90% of experimental animals. The presence of this system of veins is useful in explaining aberrant metastasis to the head, i. e., cases where no pleural involvement is seen. It probably is true that neoplastic cells can pass through the pulmonary capillaries. However, Lemoine and McLeod,[8] in their review of the subject of metastatic tumors of the choroid, reported pulmonary involvement in 83% of cases; so it is likely that metastatic tumors to the eye in most instances are seeded from the lung, at least in cases of choroidal carcinoma.

It is generally accepted that the relative infrequency of such lesions to the eye is due to the right-angled exit of the ophthalmic artery from the internal carotid artery. Smoleroff and Agatston [3] believe that the central retinal artery is involved with neoplastic emboli less frequently than is the ciliary branch, because of the fact that the exit of the ciliary branch from the ophthalmic artery makes less of a right angle than does the central retinal artery.

Among the lesions to be considered in the differential diagnosis are primary melanoma of the choroid, disciform degeneration of the macula, inflammatory lesions in the posterior segment, and the various causes of subretinal hemorrhage. The differential diagnosis of metastatic tumors to the eye in cases where a primary tumor already has been diagnosed should offer no particular problems. In our case the

appearance of the tumor when first observed simulated central chorioretinitis but the history of rectosigmoid carcinoma and the rapid enlargement of the lesion suggested its neoplastic identity. The differentiation between a choroidal carcinoma and a retinal carcinoma is at best speculative. Malignant melanoma is an important consideration in the differential diagnosis. In contrast to secondary neoplasms, primary melanoma tends to protrude into the vitreous; the location is usually, but not always, farther anterior; there is a greater tendency to glaucoma, and pigmentation usually is evident. Secondary intraocular tumors are prone to cause rapid loss of vision, to enlarge as a flat extension, and to grow rapidly, and when they are located in the choroid they are not infrequently bilateral.

When the primary source of tumor has been identified in these cases, enucleation is not urgent unless there is severe pain. Reese [13] recommended irradiation of the involved eye. Evans [16] reported a case of bilateral choroidal carcinoma that metastasized from the breast, which was successfully treated by enucleation of one eye and therapy with radon seeds over the affected part of the choroid in the other. In some cases the primary source of the metastasis is not known. Arisawa [17] reported a case in which the initial sign of carcinoma was its metastasis to the choroid and the primary rectal carcinoma was not diagnosed until autopsy a year later. Michàil [18] presented a case in which the primary symptom was similarly in the eye. He collected nine other cases, including Arisawa's,[17] in addition to his own in which the primary tumor was found after metastasis to the eye had occurred. Reese [13] reported four similar cases. In these cases of intraocular neoplasm, where there is no evident source for metastasis, enucleation is advisable because (1) the tumor may be a primary malignant melanoma and (2) histopathologic evidence may suggest a primary source for the tumor.

Summary

Metastatic carcinoma of the eye is rare, and retinal involvement alone is extremely unusual. A case of a secondary carcinoma of the retina with the primary tumor in the rectosigmoid is presented. The retinal tumor extended to the subretinal space; the lamina vitrea was intact, and no tumor cells were seen in the choroid or in the optic nerve. The tumor was histopathologically similar to the carcinoma of the rectosigmoid. In a review of the literature one other case of secondary carcinoma limited solely to the retina was found; another case was reported, but the neoplasm also involved the optic disc.

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Eye Manifestations of Chronic Vitamin A Intoxication

THOMAS K. OLIVER Jr., M.D., and WILLIAM H. HAVENER, M.D., Columbus, Ohio

Poisoning due to prolonged ingestion of large amounts of vitamin A occurs primarily in children receiving excessive vitamin dosage. Occasional cases are seen in adults because of the very high level of vitamin A used in some disorders. Apparently on an empirical basis, 1000 to 500,000 I. U. daily have been advised in treatment or prophylaxis of the common cold, acne, a variety of dermatoses with particular selection of those exhibiting hyperkeratosis, ocular diseases manifesting themselves by night blindness or corneal degeneration, and sometimes in otologic, gynecologic, renal, and enteric disorders. Indications for such use of vitamin A are not clearly established, and serious doubt exists as to the value of this type of treatment. Since 5000 to 7000 I. U. are recommended as the minimum daily requirement for adults, it is apparent that a very wide range exists between actual need and toxic levels of vitamin A.

Manifestations of vitamin A toxicity do not appear until many months of a fairly high dosage. (Enormous single doses may cause an acute rise in cerebrospinal fluid pressure, with attendant symptoms of headache, vomiting, and vertigo. These symptoms may be noted when single doses as high as 350,000 units are given an infant. Apparently shark and polar bear liver contain high concentrations of vitamin A, and acute intoxications are reported following a single meal of these livers.) Toxic symptoms include the central nervous system manifestations of increased intracranial pressure; exophthalmos; loss of hair, cutaneous rash, desquamation, and pigmentation; migrating arthritis pains, bleeding,

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Ohio State University, Department of Pediatrics (Dr. Oliver) and Acting Chairman, Department of Ophthalmology (Dr. Havener).

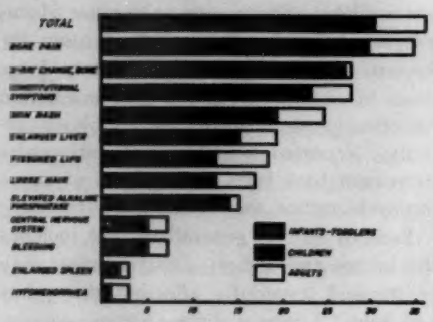

Fig. 1.—Incidence of symptoms in 36 cases summarized by Oliver.

hypomenorrhea; hepatomegaly and splenomegaly, and generalized malaise (Fig. 1).

Although not a common manifestation, central nervous system involvement is the feaure of vitamin A intoxication most likely to result in ophthalmologic consultation. The cause of increased intracranial pressure is unknown, though most authors believe it to be due to increased secretion of cerebrospinal fluid. The patient may have a typical papilledema, accompanied by the usual headaches, and sometimes develops extraocular muscle paralyses with diplopia. (Gerber reports a young woman taking 500,000 units of vitamin A daily for treatment of a skin disorder. During a period of eight and one-half years she was hospitalized 10 times in five different institutions, with diagnosis of subtentorial tumor, serous meningitis, chronic encephalitis, and infectious arthritis. Subtemporal decompression, tantalum cranioplasty, and repeated ventriculograms were done. She became totally disabled from hypertrophic arthritis and manifested all the other symptoms of vitamin A intoxication, which improved dramatically when vitamin A was stopped.) Infants may show bulging fon-

tanelles and other manifestations of internal hydrocephalus, including increased digital markings of cranial bones.

Exophthalmos is occasionally present but is not marked. It is best detected by persons familiar with the patient's previous appearance. Clinical studies of orbital tissue are not available. Speculation as to cause of this exophthalmos should take into account the known antithyroid activity of very large doses of vitamin A. Animal experimentation has clearly established this inhibitory activity. Reported limitations of extraocular movement have been on the basis of nerve paralysis rather than orbital infiltration.

Loss of hair is generalized and includes the brows and lashes. Desquamation may be marked, especially affecting the palms and soles. Often a diffuse cutaneous pigmentation develops. An itching maculopapular eruption may spread over the entire body.

The commonest manifestation of vitamin A intoxication is migrating pain and tenderness of the bones (noted in 34 of the 36 cases surveyed by Oliver). In infants this pain is often associated with noninflammatory swelling overlying the long bones. Characteristic roetgenologic findings of cortical hyperostosis and mottling are seen in children. Adults rarely show positive x-ray findings. The spontaneous fractures reported in laboratory rats do not occur in human cases.

Hypoprothrombinemia, which responds to vitamin K therapy, may cause bleeding following minor injuries or surgery. Adult females develop hypomenorrhea, which disappears promptly when vitamin A is discontinued. Hepatomegaly and splenomegaly may occur. General irritability, anorexia, and weight loss are common.

Treament of vitamin A intoxication is entirely dependent upon the recognition of the syndrome and withdrawal of vitamin A therapy. Symptoms clear spontaneously within a short period of time.

The following report describes a typical case of hypervitaminosis A.

A 14-year-old white girl was admitted to Children's Hospital on Sept. 11, 1956, with the chief complaint of leg pain of five weeks' duration. Two years prior to admission the patient developed superficial, nonpitting acne vulgaris, for which, 10 months prior to admission, 200,000 units of vitamin A daily had been prescribed by a dermatologist. Two months prior to admission she had her last normal menstrual period, succeeding ones being at the normal interval but scanty and of one day's duration. About the same time, the patient noted scaling and cracking of her lips and fissuring at the corners of her mouth, for which she used a number of salves without success. Five weeks before admission she began complaining of dull constant pain in her legs, particularly about the knees, aggravated by activity. At this time she was seen by her private physician, who directed that vitamin A be discontinued. This advice was not heeded by the patient, unbeknownst to either her family or the physician. In the month prior to admission leg pain worsened. She walked with a noticeable limp, favoring her left leg, and was unable to continue in gym activities. She observed that her scalp hair became dry in texture and fell out in large quantities with brushing. She also developed a maculopapular eruption on her trunk and desquamation of palms and soles. The family observed during this period that she manifested increasing irritability, but there were no specific symptoms of central nervous system involvement. No bleeding or bruising was noted. Appetite remained good, although the patient was on a self-imposed rather rigid diet because of the acne.

Family history was noncontributory.

Past history was essentially unremarkable. Menarche occurred two and one-half years prior to admission, and menstrual periods had been normal up to the present illness.

Physical examination. Weight, 54 kg.; height, 169 cm.; blood pressure, 130/70. Skin. The face was the site of superficial

Fig. 2.—Papilledema, as photographed at time of diagnosis of our case.

nonpitting acne vulgaris and milia. The lips were scaled and cracked, and there were fissures at the corners of the mouth. Over the trunk and to a less degree on the extremities was a fine discrete light-tan nonpruritic papular eruption. The skin was dry, and the palms and soles were desquamating in sheets. The underlying skin in these areas was delicate and thin. Nikolsky's sign was absent. The scalp hair was dry and loose. There was moderate alopecia. Pubic and axillary hair was normal. As seen in Figure 2, the typical appearance of early papilledema was present in each eye. The disc margins were completely blurred and slightly elevated, and the physiologic depression was obscured. Slight venous dilatation existed, and spontaneous venous pulsation was absent. Minimal external pressure elicited venous collapse. Fine capillary dilation was apparent on the disc surface. Glistening retinal edema encircled the disc, extending out about 1 dd. A number of fairly large and dense flame-shaped hemorrhages were clustered about the disc. Macula and periphery were completely normal. There were no visual symptoms. External ocular examination was entirely negative. (Specificially, no exophthalmos or extraocular muscle paresis existed.) Abdomen. Liver and spleen were not enlarged. Extremities: Pain and tenderness in both legs, more on the left, particularly medial and inferior to the tibial tubercle. There was no swelling, heat, or redness. There was no weakness, sensory disturbance, or reflex changes, nor were there signs of meningeal irritation. Mentation was normal to bedside testing.

Laboratory data. Hemoglobin, 12.9 gm/100 ml.; white cell count, 8050 per cubic millimeter, with a normal differential count; platelets, normal on apearance; blood urea nitrogen, 24 mg/100 ml.; CO_2, 21 mEq/liter; chloride, 102 mEq/liter; total base, 149 mEq/liter; total protein, 7.3 gm/100 ml.; albumin, 3.6 gm.; globulin, 3.7 gm/100 ml.; calcium, 10 mg/100 ml.; inorganic phosphate, 3.5 mg/100 ml.; alkaline phosphatase, 3.5 Bodansky units; cephalin flocculation, 1+; thymol turbidity, normal; cholesterol, 94 mg/100 ml.; protein-bound iodine, 9.6μg/100 ml. (Sept. 20, 1956); repeat, 4.8μg/100 ml. (Oct. 25, 1956). B. M. R., normal. Skeletal survey including long bones, spine, and skull, normal. Lumbar puncture (supine), crystal-clear fluid; initial pressure, 600 mm. H_2O; cells, 3 per cubic millimeter; sugar and protein, normal. EEG, normal. Fasting serum carotene and xanthophyll (Sept. 11, 1956), 264μg/100 ml. (normal, 75μg. to 150μg.) and 135μg/100 ml. (normal, 40μg. to 80 μg.), respectively; on Feb. 4, 1957, 195μg/100

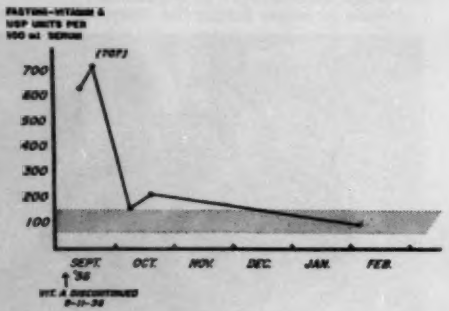

Fig. 3.—Fasting vitamin A levels. Shaded area indicates normal range.

ml. and 98μg/100 ml., respectively. The fasting vitamin A levels are shown in Figure 3.

Course. A diagnosis of chronic hypervitaminosis A was made on admission, and all medications were discontinued. Symptoms and signs began to abate within a week, and the patient was entirely asymptomatic, except for continued loose hair, after two weeks. She was discharged on Sept. 17, 1956. When examined on Oct. 6, 1956, there were no abnormalities, except that alopecia and superficial acne vulgaris (unchanged from before) were noted. Ophthalmoscopic examination was entirely normal, with no residue of the retinal hemorrhages. Regrowth of scalp hair, which was of fine texture, was not observed until six weeks after the vitamin A was stopped. Menstrual periods became normal in duration two months after medication was stopped. The patient has remained asymptomatic for nine months.

Summary

The syndrome of chronic vitamin A intoxication includes the central nervous system manifestations of increased intracranial pressure, mild exophthalmos, loss of hair including brows and lashes, cutaneous eruptions and pigmentation, migrating arthritic pains, hypoprothrombinemia, hepatomegaly and splenomegaly, hypomenorrhea, and generalized malaise.

A case of chronic hypervitaminosis A in a 14-year-old girl is presented.

The vitamin A levels were determined by Gilbert Forbes, M.D., Rochester University School of Medicine and Dentistry.

Dr. Sophie Rogers gave permission to report this case, and Prof. Jack Prince did the retinal photography.

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The Electrical Response of Human Excised Retina

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Numerous experiments have revealed the nature of the electrical response to light of excised animal eyes.[1] To our knowledge, no report exists of the recording of the ERG from the surface of the human retina.

Recently human retinal tissue immediately following enucleation has become available. Eyes removed for tumor or glaucoma which have had normal or only somewhat reduced ERG prior to enucleation have been brought to the electrophysiology laboratory within one minute following enucleation, and the retina has been subjected to study.

Methods

Immediately following enucleation a piece of retina approximately 1 cm. square was removed along with the sclera and choroid. This was done by as atraumatic a technique as possible. The tissue was placed in a sterile, clean Petri dish and covered with saline or a Ginsberg maintenance solution, ordinarily used for tissue culture. In some instances a second piece was removed; the retina, stripped from the tissue, and, as a control, recordings were attempted from the choroid and sclera alone.

Two silver-silver chloride wires, each with a terminal ball 1 mm. in diameter, were used as electrodes, put in position with a micromanipulator. One was placed on the surface of the retina; the other, on the sclera-choroid coats immediately adjacent to the retina, which was removed from the area. Two ground electrodes were placed in the bath of medium. The experimental apparatus is shown in Figure 1.

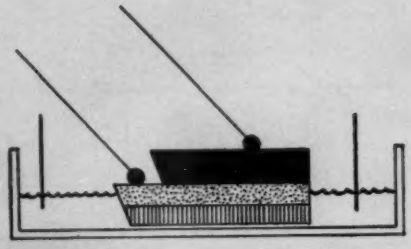

Fig. 1.—Diagram of experimental apparatus. Block of tissue with electrode on surface of retina at top. Reference electrode on surface of choroid. Ground electrodes in solution on either side of tissue block.

The electrodes were connected to the input of a Grass Model III D EEG amplifier and recorded on a pen-and-ink writer. The EMG time constant was used.

A General Radio Strobolux-Strobolux was used to supply "white light," and a special illuminator, utilizing a glow modulator tube was used to supply monochromatic filtered light. It was found possible to begin recording in about five minutes after enucleation.

Fig. 2.—Photograph of experimental apparatus, showing electrodes and retinal tissue in place.

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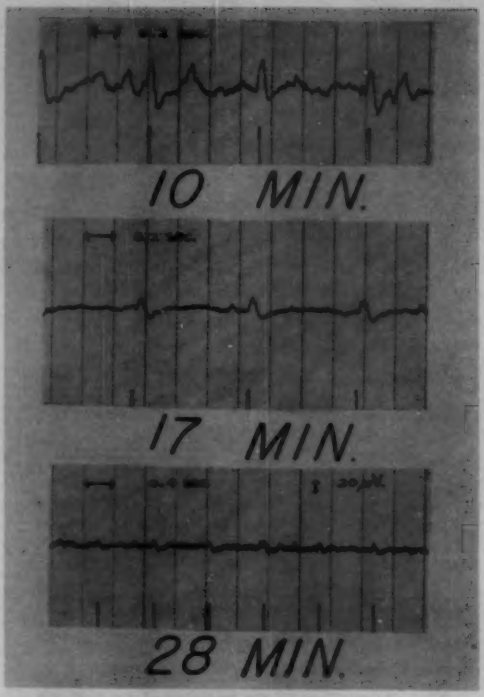

Fig. 3.—Representative tracings of responses from excised human retina, with times indicated after enucleation.

Recordings were made from a number of eyes with normal retinae and a variety of pathological states. Histological sections were made in each instance.

Results

(*a*) In one eye enucleated for malignant melanoma the retina was placed in saline. A potential of the type usually recorded from the surface of the intact globe by technique of clinical ERG was recorded. Its amplitude of positive deflection was 56μv. six minutes after enucleation. This value of the b wave gradually diminished, while the a wave remained relatively constant for 28 minutes, at which time no potential could be elicited.

(*b*) An eye removed for retinoblastoma was similarly studied, with the medium used being a tissue-culture maintenance solution. This specimen continued to produce a potential of about 54μv. for more than 60 minutes.

(*c*) Melanoma tissue from an enucleated eye produced no response.

(*d*) The effects of several drugs upon the ERG were noted. Lidocaine (Xylocaine) and procaine (Novocain) eliminated the response immediately. Lysergic acid diethylamide (LSD), a hallucinogenic drug, and hexamethonium did not alter the response. A detailed analysis of the effects of these drugs upon the ERG is in progress.

(*e*) Controls. To insure against the possibility of potentials induced by photoelectric effect upon the electrodes, causing artifacts, controls of several types were employed.

Recordings between the two ground electrodes were taken, and recordings were taken from choroid and sclera without retina. The spikes produced by the photoelectric effect in no way resembled the retinal potential.

Summary

Tracings from excised human retina following enucleation showed an electrical response to light for up to one hour. There was no response from choroid, pigment epithelium, or sclera. Lysergic acid diethylamide (LSD) did not affect the potential.

The Department of Pathology, Brittain F. Payne, Surgeon Director, and George K. Higgins, Director of Pathology, cooperated in this study.

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Changes of the Blood-Aqueous Barrier in Rabbits as a Result of Tonography

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In 1953 Friedenwald and Becker [1] published a detailed analysis of the assumptions made by Grant [2,3] when he formulated his theoretical basis for tonography. Among those assumptions was the following: "There is no change in the rate of secretion and diffusion of aqueous during tonography, i. e., flow is constant and the same as in the undisturbed eye." [1]

It was pointed out by the above-mentioned authors that small changes in flow would cause large errors in the estimation of the volume changes in the eye during tonography. For instance, a reduction in flow would result in an overestimation of the change of volume and in the coefficient of the facility of outflow.

It would therefore be of considerable theoretical interest to test the above-cited hypothesis experimentally in such a manner as to ascertain whether or not the rate of inflow and/or diffusion change during the four minutes of tonography. Unfortunately, the technical problems are very difficult, if not impossible, to overcome. The studies described below are merely an attempt to approach this problem as closely as is technically feasible.

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Methods and Material

In this study, inulin was used as a test substance, because previous studies by Swan and Hart,[4] Kinsey and Williamson,[5] and others [6,7] have pointed out that inulin is an ideal test substance in several respects. It is metabolically inert; it is a relatively large molecule (molecular weight, 5100), and it has a low coefficient of diffusion. In the undisturbed eye it does not penetrate the blood-aqueous barrier. The above investigators used the modified method of Roe [8] for inulin analysis, which is based on the pooling of aqueous samples from several eyes, a method that introduces several undesirable variables. It is for this reason that a new microcolorimetric method for the analysis of inulin in the aqueous humor of individual eyes was developed in cooperation with Dr. B. M. Pogell.[9] This method is based upon a specific reaction of ketoses with skatole and hydrochloric acid.*

* Method of Inulin Analysis: Procedure for serum. To 0.2 ml. of serum, 0.8 ml. of water and 2 ml. of 5% $ZnSO_4 \cdot 7H_2O$ are added, and immediately after, 2 ml. of 0.3 N $Ba(OH)_2$. The last reagent should be added slowly and with gentle shaking. After 15 minutes, the precipitate is removed by centrifugation. One milliliter of the clear supernatant is placed in a 1.9×15 cm. colorimeter tube. The tubes are placed in an ice bath, and 1.0 ml. of cold 0.04% skatole is added to each tube with a volumetric pipette. An 8 ml. volume of cold 30% hydrochloric acid is then added to each sample. After the contents are mixed, the stoppered tubes are placed in a water bath at 38 C for six hours. The tubes are then removed from the water bath and cooled in an ice bath. Ten milliliters of chloroform is added to each sample, and the purple reaction product is extracted into the lower chloroform layer by

(Footnote continued on following page)

The animals used in these experiments were adult male pigmented rabbits weighing on the average 2.5 kg.† The animals were on regular Sherwood-Feed pellet diet and water ad lib.

A 10% solution of purified dahlia inulin‡ was injected intravenously in such manner as to obtain blood levels above 100 mg. % during the first 20 minutes, a period which would include the 4-minute tonography. In addition, the injections provided a blood level of inulin of approximately 75 mg. % 30 minutes after tonography.

All rabbits were anesthetized with an intravenous injection of pentobarbital sodium U. S. P., 65 mg. per cubic centimeter in 10% alcohol. The amount injected was 0.5 ml. per kilogram of body weight.

Anterior chamber tapping was performed at the limbus with a sharp 27 gauge needle, with avoidance of any trauma to the iris or undue suction.

Three main groups of animals were studied. The first group was studied immediately (less than two minutes) after tonography; the second, 30 minutes after tonography, and the third, 1 hour after tonography. On the third group only, nephrectomies were performed so that an adequate inulin blood level could be maintained one hour after tonography.

Control Experiments.—The first studies consisted of control experiments which were carried out 20 minutes, 50 minutes, and 80 minutes, respectively, after the induction of anesthesia. These experiments consisted of an anterior chamber puncture of the right eye followed by an anterior chamber puncture of the left eye, which in turn was followed immediately by a cardiac puncture.

Experimental Studies.—One week later, the same animals in the first two groups were subjected to the same experiments, with the difference that a 4-minute tonography was performed on the right eye of each animal 16 minutes after the beginning of anesthesia. Immediately after the completion of tonography, aqueous tapping was performed on the right eye, followed by a tap on the left eye, followed by a cardiac puncture. The same procedure was followed on the second group, except that the tapping occurred 30 minutes after tonography. In the third group, of nephrectomized rabbits, the taps were performed one hour after tonography.

Fluorescein-Appearance Time.— In an attempt to study changes in the rate of aqueous secretion, we resorted to fluorescein. This method was first outlined by Linner and Friedenwald.[10] In a series of 13 rabbits intravenous injections of 2.5 ml. of fluorescein sodium§ were given one minute after the completion of tonography on the right eye. The animals were under pentobarbital anesthesia, and tonography was performed 16 minutes after the induction of anesthesia. Each eye was observed simultaneously by separate observers using Haag-Streit slit lamps on which cobalt blue filters had been mounted. Circulation time, i. e., ear to eye, was six seconds.

Results

First Group.—Immediately After Tonography.—Table 1 comprises the individual data of the concentrations of inulin in blood and aqueous of each eye which were obtained in the control series and in the same group of animals in the experimental series, one week later, immediately after a four-minute tonography on the right eye.

several inversions. After the layers have been allowed to separate completely and the tubes, to warm to room temperature, the optical density of each sample is read at 510 mμ in a Beckman Model B or other suitable spectrophotometer against a reagent blank. A standard of 0.018 mg. of inulin is included in each run, and results are expressed as milligrams of inulin per 100 ml. of serum.

Procedure for aqueous. One-tenth milliliter of aqueous humor is pipetted into each colorimeter tube; nine-tenths milliliter of water is added, and the samples are directly analyzed for inulin content as above.

† Purchased from The Research Supply Co., Philadelphia.

‡ All the inulin solutions used in these studies were supplied by the U. S. Standard Products Co.

§ Fluorescite (C. F. Kirk Co., New York).

TABLE 1.—*Findings in Group 1*

Animal	Control *			After Tonography †		
	Blood Inulin, Mg. %	Aqueous Inulin, Mg. %		Blood Inulin, Mg. %	Aqueous Inulin, Mg. %	
		R. E.	L. E.		*R. E.*	L. E.
1	104.30	7.7	3.80	110.00	*18.80*	17.00
2	124.00	14.0	13.00	127.50	*14.00*	14.00
3	124.30	16.50	17.20	100.50	*19.90*	20.10
4	130.00	10.30	13.50	132.00	*20.80*	20.10
5	104.00	10.40	8.90	153.50	*9.20*	10.30
6	148.50	14.60	19.20	112.00	*6.60*	10.60
7	140.50	22.00	35.00	152.50	*20.00*	40.70
8	154.00	3.30	9.30	123.30	*7.10*	12.20
9	147.50	4.40	11.00	125.40	*11.40*	19.00
10	120.40	7.70	4.40	122.30	*9.60*	10.40
11	105.60	3.30	7.70	111.00	*8.30*	13.80
12	133.50	18.70	18.70	102.00	*13.80*	16.60
13	118.00	11.40	19.30	102.80	*10.80*	18.00
14	162.00	9.10	11.30	162.70	*16.00*	9.20
15	100.00	6.20	10.20	102.00	*18.00*	8.60
16	125.30	12.00	17.00	127.50	*10.90*	8.60
Mean	127.50	10.35	13.72	124.00	13.90	16.15
Range	100.00–162.00	3.30–22.00	3.80–35.00	100.50–162.70	6.60–30.20	8.60–40.70

* Aqueous tapping was performed on this group of animals 20 minutes after the beginning of anesthesia.
† Aqueous tapping was performed on this group of animals immediately after tonography. Tonography was performed only on the *R. E.*, 16 minutes after the beginning of anesthesia. The R. E. in both groups of animals was always the first eye tapped.

Table 2 represents a summary of the statistical analyses of the findings in the first group of experiments. The results of this analysis were as follows:

TABLE 2.—*Summary of Statistical Analyses in Group 1* *

(A)		(C)	
L. E. (1)	R. E.	*R. E.*	R. E.
x=3.87	t=1.12	x=3.52	t=1.77
n=16	t=3.020	n=16	t=2.00
S. D.=4.47	P<0.009	S. D.=7.08	P<0.064
(B)		**(D)**	
L. E.(2)	L. E.(1)	L. E.(2)	*R. E.*
x=2.42	t=1.53	x=2.26	t=1.88
n=16	t=1.327	n=16	t=1.200
S. D.=6.14	Not significant	S. D.=7.63	Not significant

* Anterior chamber tapping was performed immediately after tonography, 16 minutes after anesthesia: R. E., the only eye on which tonography was performed; (1), second eye tapped in the control series; (2), second eye tapped after tonography, experimental series; x, mean of the differences; S. D., standard deviation; n, number of samples.

(A) the mean differences of inulin concentration of the left eye and right eye of the same animals in the control series

(B) the mean differences of inulin concentration of the left eye of the experimental series and the left eye of the control series

(C) the mean differences of inulin concentration of the right eye immediately after tonography and the right eye of the control series, in which no tonography was performed

(D) the mean differences of inulin concentration of the right eye immediately after tonography of the experimental series and the left eye of the control series.

Second Group—Thirty Minutes After Tonography.—Table 3 represents the individual data of the concentrations of inulin

TABLE 3.—*Findings in Group 2*

Animal	Control *			After Tonography †		
	Blood Inulin, Mg. %	Aqueous Inulin, Mg. %		Blood Inulin, Mg. %	Aqueous Inulin, Mg. %	
		R. E.	L. E.		*R. E.*	L. E.
1	67.00	10.60	5.80	72.00	*4.65*	2.30
2	56.00	9.70	11.20	57.20	*7.40*	9.60
3	87.50	6.70	9.00	100.30	*4.30*	9.20
4	106.80	20.70	30.50	135.80	*19.80*	29.50
5	77.30	13.10	9.90	75.00	*22.30*	20.50
6	70.50	20.10	29.40	82.80	*31.30*	33.40
7	70.20	11.80	13.85	73.30	*18.10*	13.60
Mean	76.40	13.24	15.66	82.10	*14.80*	16.80
Range	56.00–106.80	7.70–20.70	5.80–30.50	52.80–135.80	*4.65–31.80*	2.30–33.40

* Aqueous tapping was performed 50 minutes after the beginning of anesthesia.
† Aqueous tapping was performed 30 minutes after tonography. Tonography was performed only on the *R. E.*, 16 minutes after the beginning of anesthesia. The R. E. in both groups was always the first eye tapped.

TABLE 4.—*Summary of Statistical Analyses in Group 2* *

(A)		(C)	
L. E. (1)	R. E.	*R. E.*	R. E.
x=2.42	s=2.11	x=1.61	s=2.42
n=7	t=1.152	n=7	t=0.666
S. D.=5.57	Not significant	S. D.=6.40	Not significant
(B)		**(D)**	
L. E. (2)	L. E. (1)	L. E. (2)	*R. E.*
x=1.21	s=1.79	x=2.02	s=1.56
n=7	t=0.684	n=7	t=1.280
S. D.=4.73	Not significant	S. D.=4.37	Not significant

* Anterior chamber tapping was performed 30 minutes after tonography, 30 minutes after anesthesia. *RE*, the only eye on which tonography was performed; (1), second eye tapped in the control series; (2), second eye tapped after tonography, experimental series; x, mean of the differences; S. D., standard deviation; n, number of samples.

in blood and aqueous of each eye obtained in the control and in the experimental series, 30 minutes after tonography. The same animals were used in the control and in the experimental series.

Table 4 consists of a summary of the statistical analyses of the findings in the second group of experiments. A, B, C, and D represent comparisons similar to those described in the first group of experiments (above).

Third Group—One Hour After Tonography.—Table 5 represents the individual data of the concentration of inulin in blood and aqueous of each eye of a control series of nephrectomized rabbits and in another group of nephrectomized rabbits representing the experimental series one hour after a four-minute tonography.

Table 6 is a summary of the statistical analyses of the findings in the third group of experiments, following the same method and order of statistical evaluation of the differences of inulin concentration found in each eye which was previously described for A, B, C, and D under the first group.

TABLE 5.—*Findings in Group 3*

	Control *				After Tonography †		
		Aqueous Inulin, Mg. %				Aqueous Inulin, Mg. %	
Animal	Blood Inulin, Mg. %	R. E.	L. E.	Animal	Blood Inulin, Mg. %	*R. E.*	L. E.
1	95.00	7.00	7.00	1	168.10	*10.80*	19.60
2	123.00	1.85	2.90	2	180.00	*20.80*	30.50
3	125.00	15.00	9.50	3	107.20	*0*	0
4	95.00	9.00	11.00	4	102.40	*11.00*	0
5	102.00	12.00	15.00	5	107.20	*0*	4.80
6	124.00	7.00	14.00	6	134.25	*8.45*	5.80
				7	107.00	*16.40*	16.40
				8	100.00	*6.00*	5.80
Mean	110.60	8.64	9.90	Mean	125.80	*9.19*	10.36
Range	95.00–124.00	1.85–15.00	2.90–15.00	Range	102.40–180.00	*0–20.80*	0–30.50

* Control and After Tonography are two different groups of nephrectomized rabbits. Experiments were performed on those anim mals 24 hours after nephrectomy. Aqueous tapping was performed on the control group of animals 80 minutes after the beginning o anesthesia. R. E. was always the first eye tapped. Tonography was performed only on the *R. E.*

† Aqueous tapping was performed on this group of animals one hour after tonography.

TABLE 6.—*Summary of Statistical Analyses in Group 3* *

(A)		(B)	
L. E. (1)	R. E.	*R. E.*	R. E.
x=0.99	s=1.66	x=9.19±3.46	x=8.33±3.46
n=6	t=0.599	n=8; n=6	t=0.216
S. D.=4.110	Not significant	S. D.=0.41	Not significant
(B)		**(D)**	
L. E. (2)	L. E. (1)	L. E. (2)	*R. E.*
x=10.36±4.58	x=9.33±4.58	x=1.17	s=2.30
n=8 (2); n=6 (1)	t=0.445	n=8	t=0.469
S. D.=6.48	Not significant	S. D.=6.78	Not significant

* Anterior chamber tapping was performed 60 minutes after tonography, 90 minutes after anesthesia. *R. E.*, the only eye on which tonography was performed; (1), second eye tapped in the control series; (2), second eye tapped after tonography, experimental series; x, mean of the differences; S. D., standard deviation; n, number of samples.

Fourth Group.—A different series of animals, consisting of 13 rabbits, was studied by means of the fluorescein-appearance-time technique immediately after the completion of a four-minute tonography on the right eye. The mean values of this group are presented in Table 7.

TABLE 7.—*Fluorescein-Appearance Time One Minute After Tonography* *

	R. E. (Tonography)	L. E. (No Tonography)
Mean and S. E.	60.75±3.88	62.10±4.70
Rabbits, No.	13	13
Standard Deviation	13.43	16.57

* Circulation time of six seconds.

Comment

It is of interest to note that in our control series (Table 1), in which the eyes were undisturbed except by the puncture, an average aqueous inulin concentration of 10 mg. % was found in the individual samples. This is at variance with previous reports by Duke-Elder[6] and Swan and Hart,[4] who detected only traces of inulin in pooled aqueous samples. It seems possible that the levels of inulin found in the undisturbed eye in our study were due to a more sensitive technique used. However, the chances that any significant amount of inulin would get through the undisturbed barrier would seem to be very small, particularly in view of the inulin blood levels used in our experiments.

It can be seen from Table 2(C) that the aqueous inulin concentration in the eye immediately after tonography was found to be significantly higher than in the same eye before any tonography was performed ($P<0.064$). It is worthy of emphasis, however, that an increased permeability of the blood-aqueous barrier to inulin immediately after tonography does not necessarily prove that such a change in permeability had actually occurred during tonography. Nevertheless, the implication is strong that in rabbits the permeability of the blood-aqueous barrier to inulin is increased at least toward the end of the four-minute tonography.

The above inulin data, per se, do not give any direct information about any possible changes of aqueous secretion, and it was primarily for this reason that we resorted to the technique of determining fluorescein-appearance time. It is important to reemphasize that the basic assumption made in the determination of aqueous flow by this technique is that the fluorescein which appears in the posterior chamber arrives there solely on the basis of secretion. It can be seen from Table 7 that the fluorescein-appearance time immediately after tonography did not differ significantly from that in the control eye, on which no tonography was performed. Also, these values are in good agreement with those reported previously by Linner,[10] Prijot and Stone,[11] and others who found that the normal fluorescein-appearance time in rabbits averaged about 60 to 65 seconds.

The change in the permeability of the blood-aqueous barrier which could be demonstrated immediately after tonography was no longer detectable 30 minutes or 60 minutes after tonography by the inulin technique. It is interesting that no significant increase in the permeability of the barrier was found in nephrectomized rabbits, as this was recently suggested by Langham.[12] However, another test substance was used in his investigation.

The data in Table 2(A) indicate that the permeability of the blood-aqueous barrier to inulin was increased in the second eye after anterior chamber puncture on the first eye. The time interval between the puncture of the first and of the second eye averaged about two minutes. This type of consensual reflex affecting the permeability of the blood-aqueous barrier has been demonstrated with different methods by several previous investigators.[13-15] In contrast to these findings, no significant change in the permeability of the barrier was found in the second, nontonographed, eye following tonography on the first eye [Table 2(D)].

Summary and Conclusions

By the use of a newly developed micromethod for inulin analysis in individual aqueous samples, a measurable increase in the permeability of the blood-aqueous barrier of rabbit eyes was found immediately after the completion of tonography.

Using inulin as a test substance, it was possible to corroborate the findings of previous investigators that a puncture of one eye in rabbits results in a reflex increased permeability of the blood-aqueous barrier in the fellow eye.

Fluorescein-appearance-time studies revealed no significant change in the rate of

aqueous formation immediately after tonography.

An increased permeability of the blood-aqueous barrier immediately after tonography, per se, does not prove that a similar condition exists during tonography, but the implication is strong.

Until more data are available, conclusions with respect to the changes of permeability of the blood-aqueous barrier in rabbits as a result of tonography do not warrant similar conclusions with respect to clinical tonography.

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Effects of Superior Cervical Ganglionectomy on Aqueous Humor Dynamics

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Various studies have been performed previously by several investigators regarding the relationship between the sympathetic nervous system and intraocular pressure. Out of such studies has come much controversy involving the effects of different types of anesthesia used by various investigators. Through the use of local anesthesia in a particular phase of our experiment, we have endeavored to arrive at certain values by tonographic measurements which, apparently, were not obtainable under similar experimental conditions when general anesthesia was employed.

Early reviews were made by such investigators as Thiel,[16] Magitot,[11] and Duke-Elder.[2] Such studies were also made at a later date by Weinstein.[17] Loewenstein and Schoenberg[14] concluded from pupillographic studies that the central sympathetic factor plays a definite role in the beginning of primary simple glaucoma. Jaffe,[6] in later experiments, produced a drop in intraocular pressure in the eyes of cats following cervical sympathectomy operations.

Following sympathetic ganglionectomies on rabbits, Linnér and Prijot[10] were unable to perform tonography on the eye situated on the operated-on side on the first postoperative day, because the pressure was so low that the instrument went off scale. Therefore, the coefficient of facility of outflow and intraocular pressure were measured after enucleation by means of a perfusion technique. No values were reported for the flow on the first day following the operation. However, they stated that since no significant difference occurred between the facility of outflow on the side operated on and the facility on the intact side, obtained after enucleation by the perfusion technique, an outflow pressure close to zero indicated a decreased rate of aqueous flow. For their tonographic measurements, Linnér and Prijot administered paraldehyde (1.5 cc. per kilogram) by a stomach tube as a general anesthetic. Rubino and Esente[12] reported that barbiturates lowered intraocular pressure by "paralysis" of the diencephalon. Lieb and Scherf[8] found that six of the opium alkaloids decreased intraocular pressure (morphine, thebaine, protopine, laudanosine, cryptopine, and rhoeadine) and that three caused an increase in intraocular pressure (codeine, papaverine, and narcotine). The Corydalis alkaloids which were tested (bulbocapnine, corydine, and corybulbine) caused an increase in pressure. In a third group of alkaloids, glaucine acted indifferently and berberine decreased the pressure, whereas sanguinarine and chelidonine increased intraocular pressure. It was suggested that pathophysiological phenomena such as narcotic effects, motor restlessness, tetany, incoordination of movements, or postural imbalances, as well as vascular and circulatory disturbances, salivation, and mydriasis, could mainly be accounted for by the effects of the alkaloids on the extrapyramidal system, as well as on the diencephalon. It was further suggested that, in view of these symptoms, intraocular pressure changes could also have their origin in the same above-men-

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tioned centers. A more direct approach, to investigate the importance of the diencephalon as a pressure-regulating area, was made by von Sallmann [13] and co-workers in their studies of the electrical stimulation of the midbrain in cats. In an effort to determine whether, and to what extent, general anesthesia induces changes in the dynamics of the aqueous humor, Stone and Prijot [15] later discovered that the intraocular pressure in animals anesthetized with paraldehyde was lower than the value obtained without general anesthesia. However, the values were found to be even lower for pentobarbital sodium than for paraldehyde anesthesia. Subsequent studies by Becker and Constant [1] showed that tonography could be successfully performed on rabbits with topical anesthesia only.

To investigate the possibility that pressure, facility, and flow values could be obtained by means of tonography on the first day after superior cervical ganglionectomy, we employed local anesthesia in the following experiment, in order to prevent the influence of general anesthesia on the aqueous dynamics.

Method

Sixteen male pigmented rabbits, weighing 2 to 3 kg., were chosen for the experiment. Several control tonographies were performed on these rabbits prior to the beginning of the actual experiment (1) in order to obtain a group of normal rabbits and (2) in order to accustom the group of rabbits to the tonographic procedures. The rabbits were wrapped very tightly in a sheet in order to immobilize them, and several drops of 0.5% tetracaine (Pontocaine) hydrochloride were applied to each cornea as local anesthesia. Then, with care in handling the animal in order to avoid excitement, the intraocular pressure was measured by means of an electronic tonometer (V. Mueller & Co.), with use of Grant's [5] method of tonography. Tracings of each tonography were made with the Sanborn Twin-Viso recorder in conjunction with the V. Mueller Electronic Tonometer. Measurements were made in the following order: first, tonometry on the right eye and then tonometry on the left eye; second, tonography on the right eye and then tonography on the left eye. The tables of Friedenwald [3] (1954) were used for the calculations. One day after the final control reading, the superior cervical ganglion was removed successfully from the right side in 12 rabbits, with the animals under general anesthesia (pentobarbital sodium, 65 mg. per cubic centimeter; 0.5 ml. per kilogram of body weight). The operative result was questionable in the remaining four rabbits. These animals were therefore omitted from further studies. The superior cervical ganglion is a slightly bulging structure extending posteriorly from just behind the common carotid artery and slightly anterior to the mandibular joint. It may be located by tracing the sympathetic nerve anteriorly to a position slightly beyond the mandibular joint.

The sympathetic nerve lies within the carotid artery sheath, and, therefore, extreme care must be exercised that the carotid artery is not handled while the nerve is separated and traced. Handling of the carotid artery, with possible resultant thrombosis, could in itself cause a drop in the intraocular pressure on the side operated on. Kornbluth and Linnér [7] observed a drop in intraocular pressure accompanied by a decrease in the facility of outflow on the side operated on following unilateral ligation of the carotid artery in rabbits. So, in order to assure ourselves, in our experiment, that our measurements were not influenced by thrombosis or any other obstruction of the lumen of the carotid artery, we did arteriograms subsequent to the experiment. No evidence of an obstruction was found.

On the day following the superior cervical ganglionectomies, postoperative tonographic measurements were begun. Tonographic measurements were per-

formed each day for a period of 15 postoperative days.

Results

From the 12 animals operated on successfully, the preoperative tonographic tracings showed for the right side a mean intraocular pressure of 27.52 mm., a mean facility of 0.22 cu. mm. per minute per millimeter of Hg, and a mean flow of 3.93 cu. mm. per minute. For the left side, there were a mean intraocular pressure of 25.77 mm., a mean facility of 0.22 cu. mm. per minute per millimeter of Hg, and a mean flow of 3.63 cu. mm. per minute. There was no significant difference between the right and left eye measurements.

On the first postoperative day the mean intraocular pressure (P_o) on the right, or operative, side was 11.93 mm. Hg, as compared with a mean intraocular pressure of 27.31 mm. Hg on the left, or intact, side. There was a mean facility of 0.21 cu. mm. per minute per millimeter of Hg on the side operated on and a mean facility of 0.22 cu. mm. per minute per millimeter of Hg on the side not operated on. The mean flow measurements were 0.63 cu. mm. per minute on the side operated on and 3.64 cu. mm. per minute on the side not operated on.

On the second postoperative day the intraocular pressure (P_o) had practically returned to normal in all cases (O. D. P_o =27.23 mm.; O. S. P_o=25.43 mm.), but the facility was slightly lower in both eyes (O. D. C=0.18; O. S. C=0.18).

By the third postoperative day all values had returned to normal. Further tonographic measurements revealed normal values throughout the remaining 12 days of the experiment.

The steady state of aqueous flow (F) was determined by employing the formula $F=C(P_o-P_v)$. F represents aqueous flow in cubic millimeters per minute; C,

*Mean Tonographic Results of Superior Cervical Ganglionectomies on Twelve Pigmented Rabbits**

Postoperative Day	Right Eye			Left Eye			t
	P_o (S. E.)	C (S. E.)	F (S. E.)	P_o (S. E.)	C (S. E.)	F (S. E.)	
Control	27.52 (0.514)	0.22 ----	3.93 (0.341)	25.77 (0.526)	0.22 ----	3.63 (0.141)	P_o=2.38 C =.... F =0.535
1	11.93 (0.321)	0.21 (0.0091)	0.63 (0.0710)	27.31 (0.500)	0.22 (0.0100)	3.64 (0.295)	P_o=18.73 C =0.769 F =8.22
2	27.23 (0.488)	0.18 ----	3.29 (0.155)	25.43 (0.569)	0.18 ----	2.95 (0.168)	P_o=2.41 C =.... F =1.49
3	28.25 (0.389)	0.22 (0.0082)	4.16 (0.145)	26.74 (0.370)	0.23 (0.0091)	4.02 (0.175)	P_o=2.78 C =0.780 F =0.614
5	27.87 (0.413)	0.23 ----	4.35 (0.198)	26.38 (0.384)	0.23 ----	4.07 (0.183)	P_o=1.67 C =.... F =0.470
7	28.06 (0.361)	0.23 (0.016)	4.40 (0.208)	26.47 (0.428)	0.24 (0.016)	4.21 (0.201)	P_o=1.79 C =0.056 F =0.296
9	28.07 (0.439)	0.22 (0.0095)	4.24 (0.209)	26.57 (0.408)	0.23 (0.0078)	4.00 (0.136)	P_o=1.63 C =0.076 F =0.408
11	27.86 (0.436)	0.22 (0.0029)	4.21 (0.176)	26.29 (0.390)	0.23 (0.0067)	3.88 (0.505)	P_o=1.75 C =0.091 F =0.400
13	28.27 (0.408)	0.23 (0.009)	4.42 (0.193)	26.76 (0.402)	0.24 (0.008)	4.32 (0.149)	P_o=1.57 C =0.077 F =0.170
15	28.35 (0.338)	0.23 (0.008)	4.43 (0.170)	26.93 (0.413)	0.24 (0.008)	4.32 (0.165)	P_o=1.64 C =0.080 F =0.189

* P_o, closed or initial intraocular pressure; S. E., standard error of the mean; C, facility of outflow; F, rate of aqueous flow; t, limit of probability at 0.01 level.

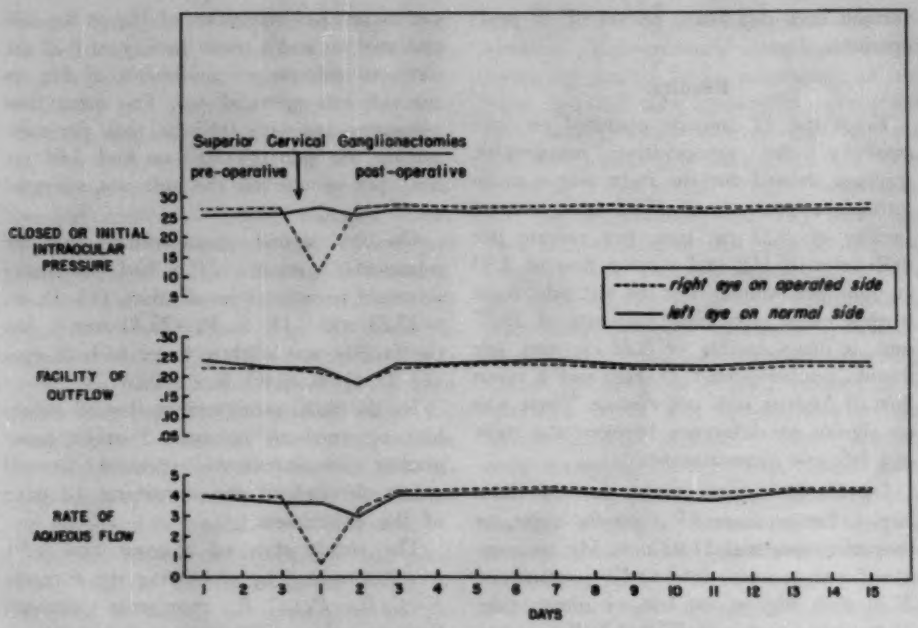

Fig. 1.—Mean differences between right and left eye tonographic measurements of intraocular pressure, facility of outflow, and rate of flow, following superior cervical ganglionectomies.

coefficient of facility of outflow; P_o, initial intraocular pressure in millimeters of Hg; P_v, episcleral venous pressure of 9.0 mm. Hg, as determined by Linnér[9] for rabbits.

Comment

On the first day after the superior cervical ganglionectomy the intraocular pressure on the side operated on dropped markedly, to the extent that the difference between the P_o on the side operated on and the P_o on the side not operated on was highly significant. Also, a significant decrease in the flow was manifested on the side operated on, but no significant difference occurred between the facilities on the right and left sides. In light of an experiment performed by Friedenwald and Buschke,[4] wherein they produced an inactivation of the secretory mechanism in the eyes of rabbits, followed by reactivation after the administration of epinephrine, a neurological relationship between the adrenergic system and introcular pressure might be suggested.

On the second postoperative day there was no significant difference between the measurements of intraocular pressure, facility, or flow between the right and left eyes. However, there was a slight decrease in the measurement of facility and rate of flow in both eyes.

By the third postoperative day there was no significant difference between any of the values for both eyes, and subsequent measurements of intraocular pressure were normal for the remaining 12 days of the experiment.

Summary

Following the removal of the superior cervical ganglion in a group of 12 pigmented male rabbits, changes in aqueous dynamics were noted.

Through the use of proper immobilization techniques and local anesthesia, we were able to obtain tonographic measure-

ments on the first postoperative day, which showed that there occurred a significant decrease in the intraocular pressure and of the rate of flow on the side operated on. No significant changes occurred in the facility of outflow. Further studies up to a period of 14 days revealed that normal values for intraocular pressure, facility, and flow were restored within a period of from two to three days postoperatively.

The changes observed on the first postoperative day were essentially the same as those obtained by Linnér and Prijot on the enucleated eye by means of perfusion technique.

Medical College of Virginia.

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The Effect of the Tonometer Footplate Hole on Scale Reading

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It has been noted in this laboratory[1] that tonograms starting with scale readings less than 3 gave values for the intraocular pressure (P_o) and outflow facility (C) which were often higher than anticipated from the clinical findings in these patients. Furthermore, P_o and C values obtained on the same eye with a greater plunger load and a larger initial scale reading gave more reasonable, lower estimates of C and P_o. Kronfeld independently pointed out[2] that at low scale readings (high intraocular pressure) comparative measurements with the 5.5 and 7.5 gm. weights give results inconsistent with the 1955 Friedenwald tables. Clinically this problem has been resolved in most tonography laboratories and offices by using a sufficient plunger load to obtain an initial scale reading greater than 3.

These findings stimulated us to search for the source of the discrepancies, and on theoretical grounds it was decided to investigate the influence of the diameter of the hole in the Schiøtz tonometer footplate upon scale reading.

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Methods and Results

The influence of the diameter of the hole in the tonometer footplate has been studied from essentially three different approaches: (1) by comparing clinical P_o values obtained with the 5.5 and the 7.5 gm. weights in the same patient; (2) by varying the diameter of the hole in the footplate and studying the effect of such variations on (*a*) clinical P_t values and (*b*) P_t measurements in enucleated human and rabbit eyes, and (3) by direct observation of the cornea and tonometer plunger through a clear plastic footplate.

METHOD 1.—Since early in 1957 the technicians in the tonography laboratory of this institution have been instructed not to perform tonography if the initial scale reading is less than 3 but to immediately apply the next higher plunger load until the initial scale reading is 3 or greater. Thus, the tonography files provided us with many paired 5.5 and 7.5 gm. scale readings taken on routine tonographic examination. These data were augmented with initial readings of 5.5 gm. and 7.5 gm. tonographic values obtained on normal volunteers. These latter data were not obtained at one sitting but at the same hour on different days.

Results 1.—Figure 1 is a plot of P_o values obtained with the 5.5 versus the 7.5 gm. weight of the Mueller electronic Schiøtz tonometer in 80 instances. There is a lack of correspondence between P_o values in all cases where the scale reading with the 5.5 gm. weight was less than 2; all such cases showed an apparently higher P_o value with the 5.5 gm. weight than with the 7.5 gm. weight.

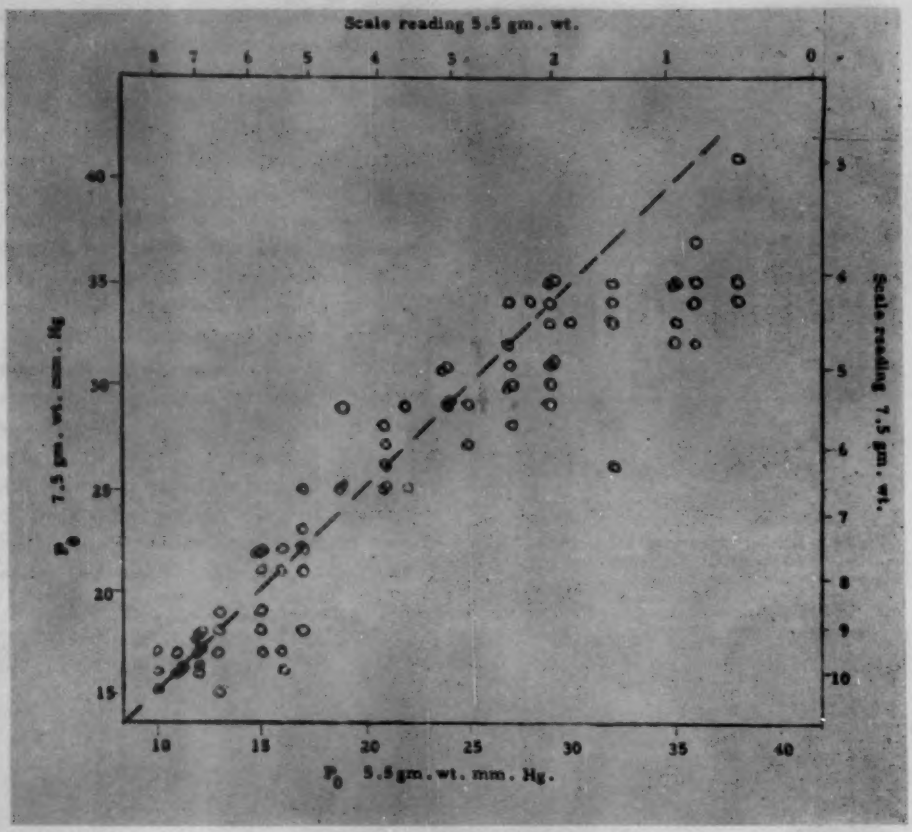


Fig. 1.—P_o as determined with 5.5 gm. weight compared with P_o as determined with the 7.5 gm. weight.

METHOD 2.—The diameter of the footplate hole was varied by means of methacrylate (Lucite) sleeves which were accurately fitted to the hole and ground to conform to the curvature of the footplate (Fig. 2). The hole in the particular Mueller electronic Schiøtz tonometer we used was 3.90 mm. in diameter. On addition, these sleeves of 3.1 and 3.3 mm. allowed us to explore the effects of three different hole sizes. In most cases, only the smallest and largest holes were used.

METHOD 2a.—Tonometric measurements were made on eyes of clinic patients first with the sleeve having the smallest inside diameter inserted in the footplate. Then the sleeve was withdrawn, and the eye was measured again with no sleeve in place. We adopted this procedure so that any pressure-lowering effect of the first tonometry would prejudice the data against a lower scale reading measurement on the second reading. The P_t value for the sleeveless second reading was obtained from the 1955 Friedenwald tables, and the P_t value for the first reading (with sleeve) was subtracted from it. These differences are plotted in Figure 3 as apparent change in P_t on withdrawing the sleeve versus the first scale reading.

Results 2a.—In all cases in which the initial scale reading was less than 3 with the small hole sleeve in place the scale reading decreased upon withdrawal of the sleeve, giving an apparent increase in P_t.

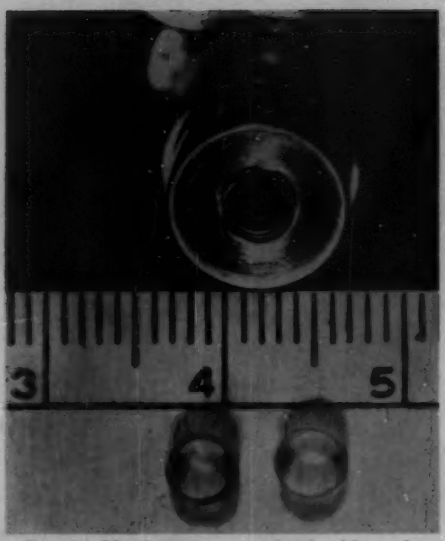
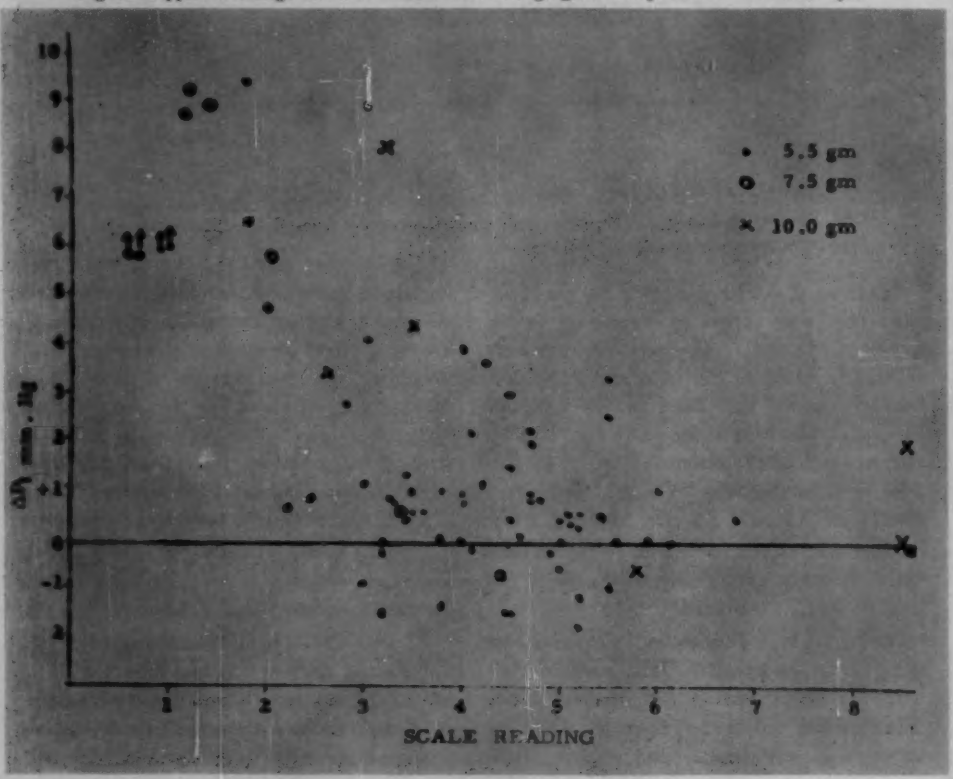


Fig. 2.—Mueller tonometer head with a sleeve inserted into footplate hole (protruding). Two other sleeves are shown below.

METHOD 2b.—Enucleated human eye bank and rabbit eyes were cannulated with a 22-gauge needle, connected through flexible tubing to a simple water reservoir. Cannulation was posterior to the limbus into the anterior chamber. The eyes were supported, cornea up, on wet raw cotton. Measurements were made with the electronic Schiøtz tonometer used in Method 2a with various plunger weights, at various heights of the water level above the corneal dome, and with various sleeves inserted.

Results 2b.—In all cases, with all plunger weights, at higher pressures scale readings tended to be lower the larger the hole size was (Fig. 4, 5, and 6). With the 5.5 gm. plunger load, there ceased to be very much difference in scale reading subsequent to change in hole size at about Scale 3 and greater in human eyes. There was not a

Fig. 3.—Apparent change in P_t coincident with enlarging the footplate hole. Patients' eyes.



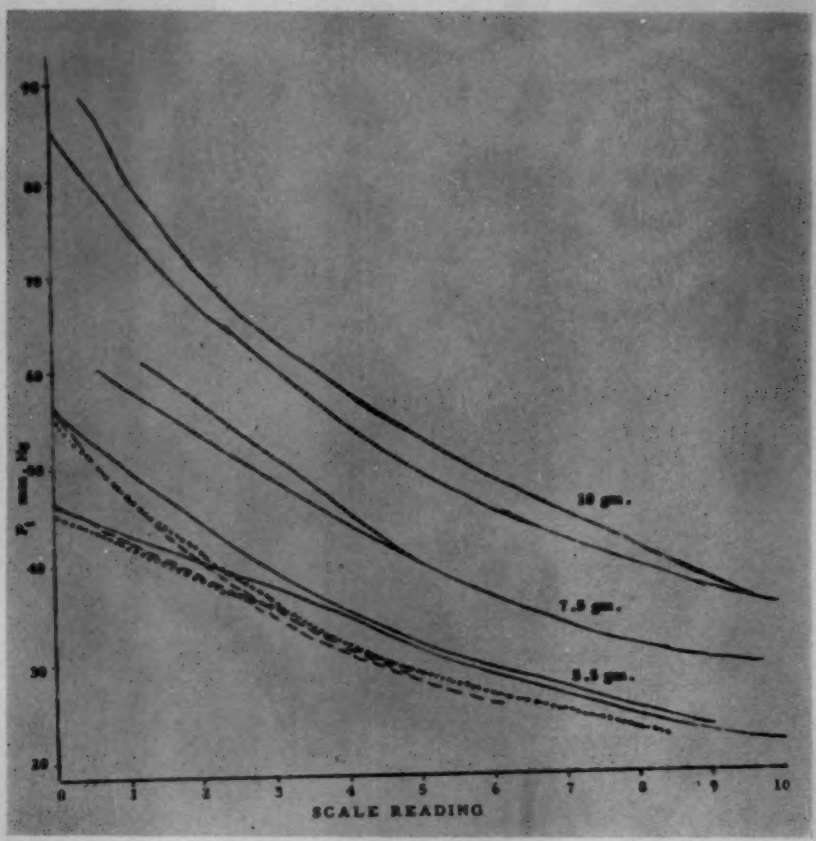


Fig. 4.—P_t (open manometer) versus scale reading, enucleated human eyes, with 10 gm. weight, one eye; 7.5 gm. weight, one eye; 5.5 gm. weight, three eyes. The upper curve in each weight group represents values obtained with the smallest footplate hole; the lower curve, with the largest.

significant change beyond Scale 4 in rabbit eyes.

The increase in P_t necessary to obtain equal scale readings incident to narrowing the footplate hole is plotted in Figures 6 and 8.

METHOD 3.—A methacrylate footplate was constructed in dimensions which corresponded closely to those of the standard Schiøtz tonometer (Fig. 10). It was appropriately weighted. The diameter of the hole in the footplate was 4 mm. The plunger was from a Mueller electronic tonometer. Observations were made with a slit-lamp microscope on cannulated enucleated human (eye bank) and rabbit eyes and on eyes of human volunteers.

Results 3.—In all cases when the footplate without plunger is on the eye, the cornea is seen to bulge into the central hole (Fig. 11). In enucleated eyes at high pressures, corresponding to scale readings of 0 to 2, the cornea can be distinctly seen to bulge into the gap between footplate and plunger. At these pressures, the doughnut-shaped dome of the cornea lies at a higher level than the footplate curve (Fig. 12).

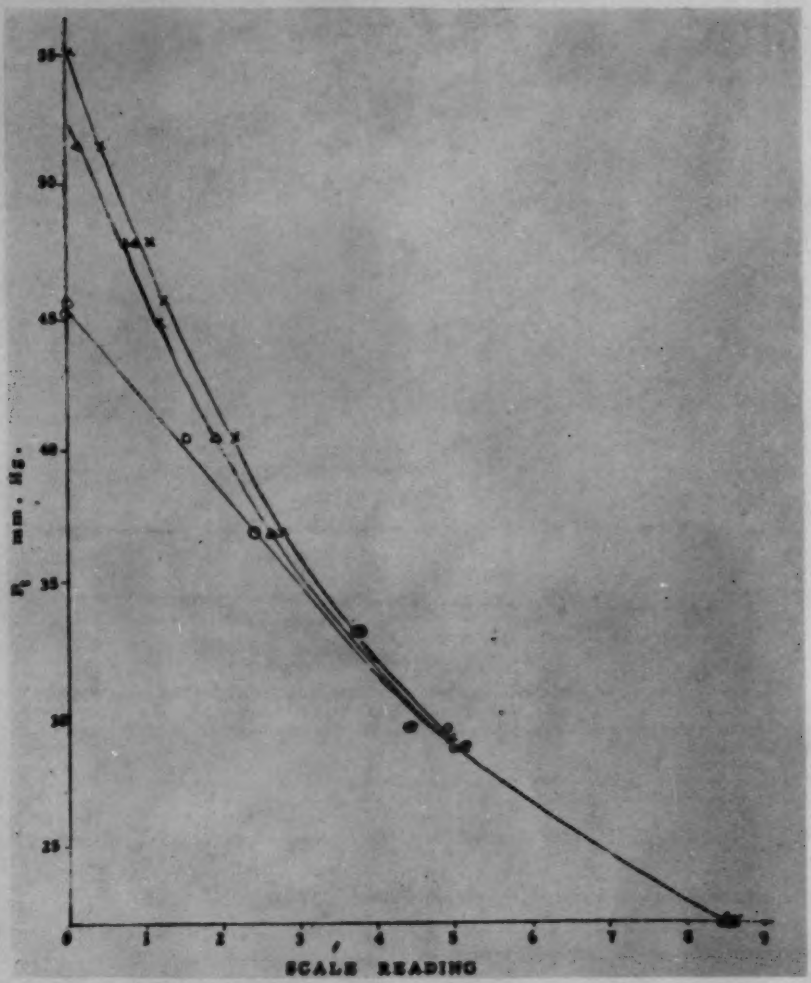


Fig. 5.—P_t versus scale reading with 5.5 gm. weights, one enucleated human eye. The upper curve represents results with the 3.1 mm. hole; the center curve, the results with the 3.3 mm. hole, and the lower curve, the results with the 3.9 mm. hole in the footplate.

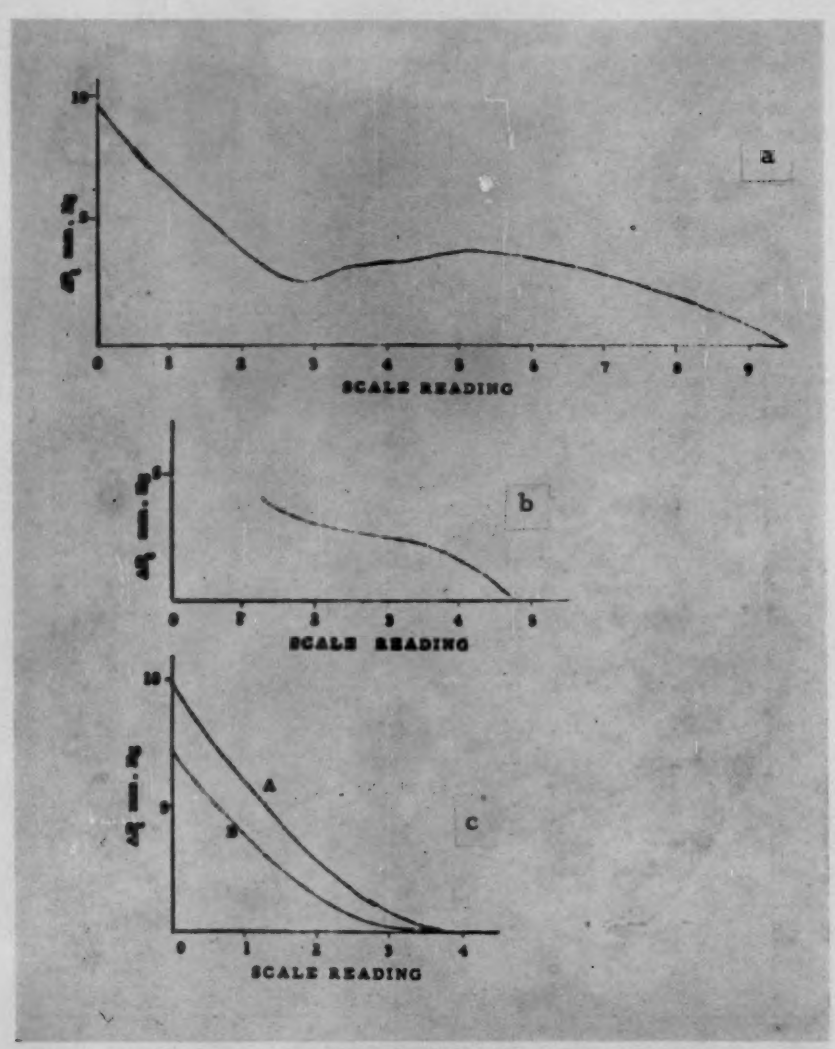


Fig. 6.—(*a*) Increment of pressure required to achieve equal scale reading on reducing footplate hole from 3.9 to 3.1 mm., 10 gm. plunger weight; (*b*) same as *a*, but for 7.5 gm. plunger load; (*c*) same as *a*, but for 5.5 gm. plunger load and footplate hole diameters of 3.1 mm. (Curve *A*) and 3.3 mm. (Curve *B*).

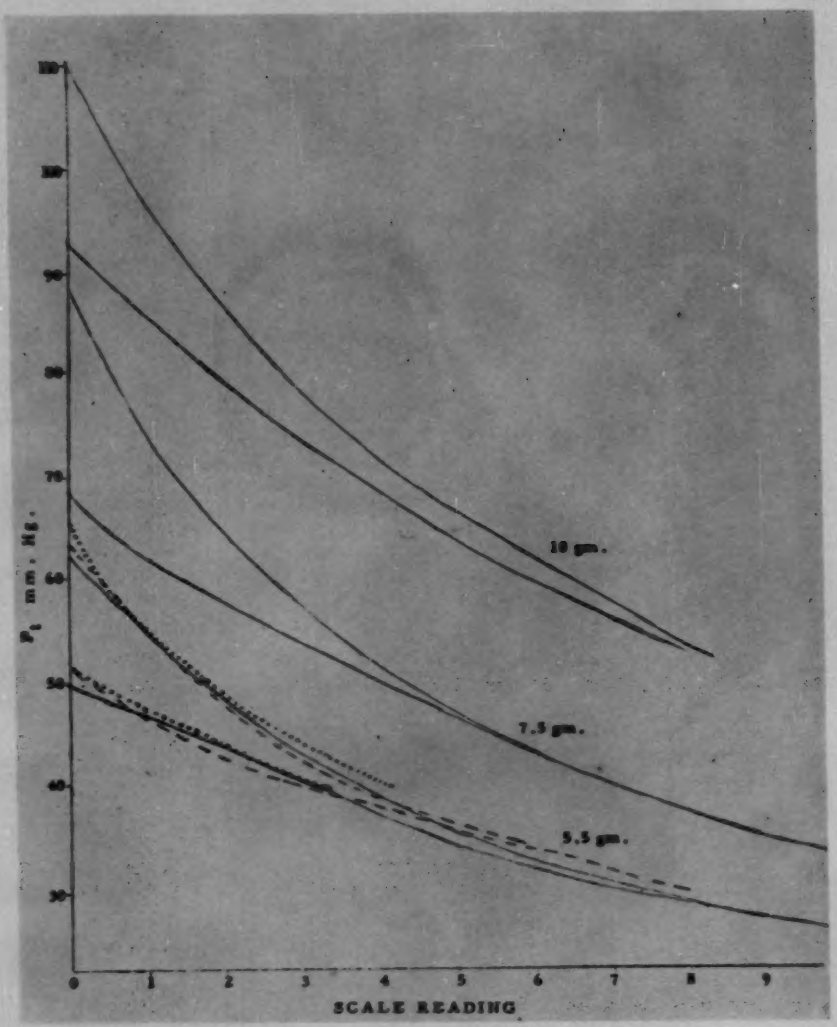


Fig. 7.—Same as Figure 4, but for rabbit data.

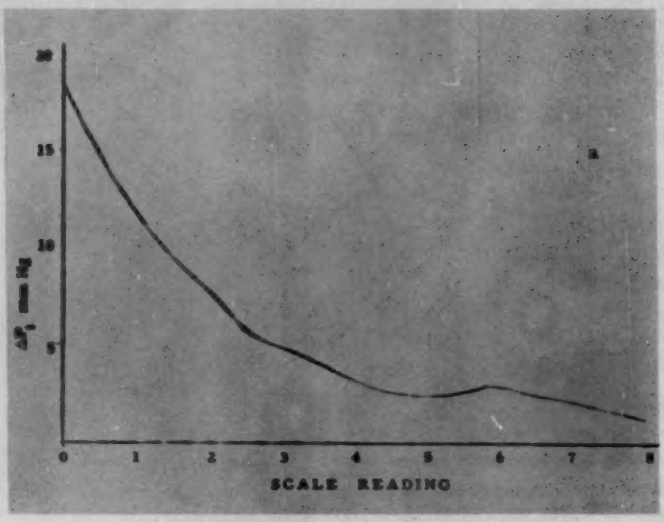
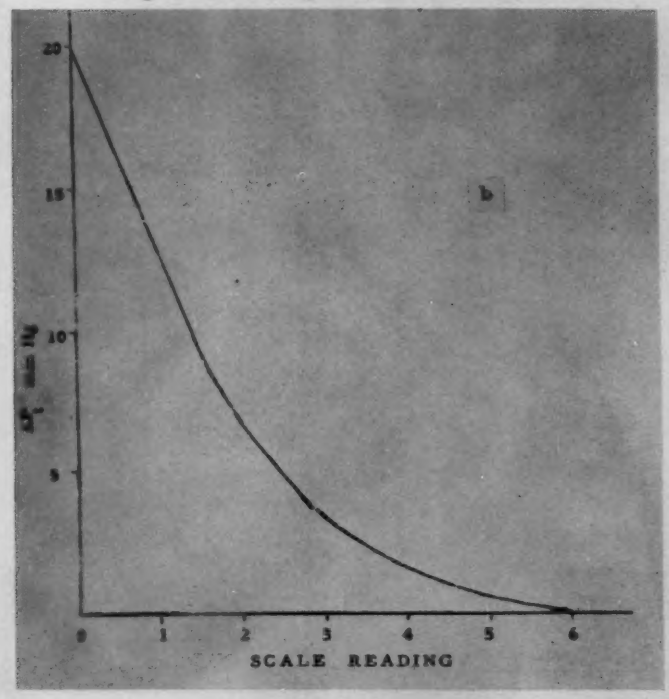


Fig. 8*a*.—Same as Figure 6*a*, but for rabbit data.

Fig. 8*b*.—Same as Figure 6*b*, but for rabbit data.



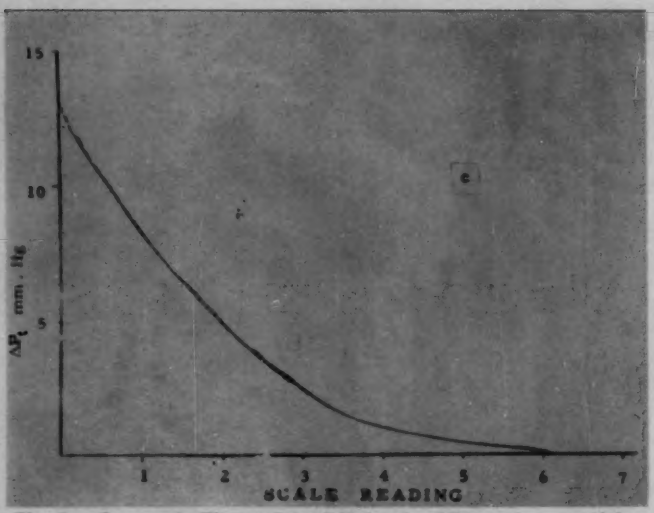
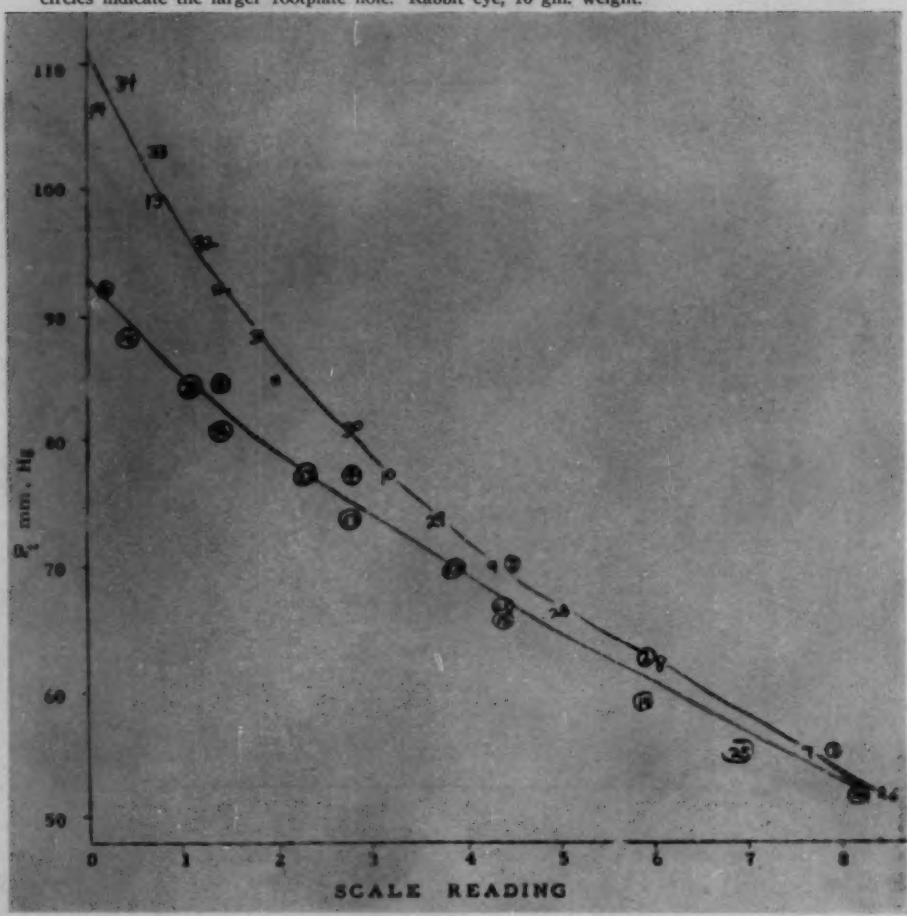


Fig. 8*c*.—Same as in Figures 8*a* and 8*b* but for 5.5 gm. plunger weight.

Fig. 9.—A typical experiment showing order in which measurements were made. The determination numbers are plotted at the appropriate locations. Those numbers enclosed in circles indicate the larger footplate hole. Rabbit eye, 10 gm. weight.



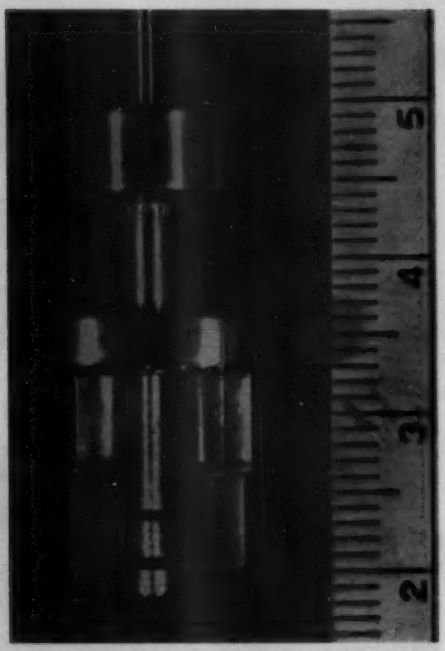


Fig. 10.—Methacrylate footplate with brass weight and Mueller plunger.

Comment

In 1954 the Committee on Standardization of Tonometers remarked that tonometers received for checking had footplate holes varying from 3.2 to 4.0 mm. in diameter.[3] Neither on the list of tests as suggested by this committee nor on the certification forms is this subject mentioned. The reason for the lack of interest in this particular feature of the tonometer probably stems from the many published diagrams such as in Figure 13,[4] in which the gap between footplate and plunger appears negligible. However, in a scale drawing of a tonometer it is seen that at low scale readings this gap is large compared with plunger protrusion (Fig. 14). We have shown that at low scale readings the cornea actually bulges into the gap, rising to a level higher than the footplate curve. Thus, part of the cornea which supports the plunger lies above the footplate at low scale readings.

The entire theory of the Schiøtz tonometer rests upon the flattening of a corneal portion by the footplate and the measurement of the depth to which a plunger sinks into this flattened area. It is clear that in the case of our tonometer, at low scale readings, the plunger is not sinking into a flattened area but into a domed one. The sleeve inserts extend the footplate and tend to flatten the bulged cornea to the level of the footplate and to lower the base of the indentation and thus its apex where the plunger rests as well. That is, at a given P_t the plunger will protrude further past the footplate and the consequent scale reading will be greater if the hole in the footplate is small. Stated conversely, when the hole in the footplate is small, a greater P_t is necessary to obtain the same scale readings as are indicated with a larger footplate hole.

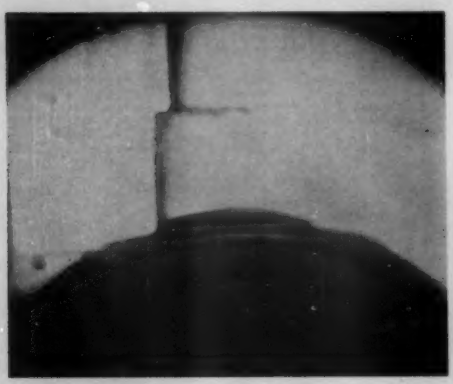
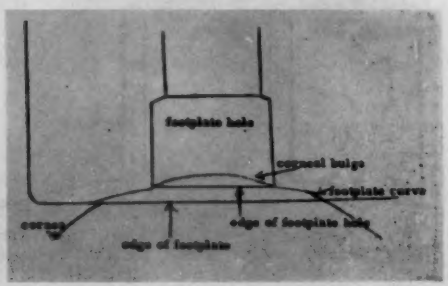
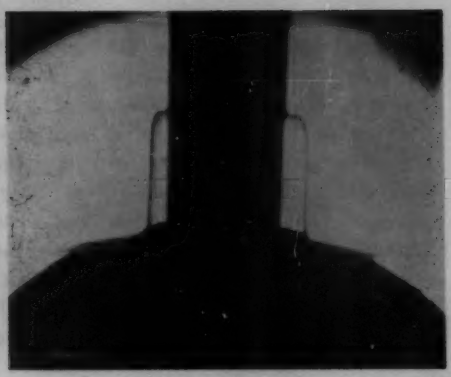


Fig. 11.—Cornea as seen through transparent footplate. Plunger not in place. Rabbit eye.





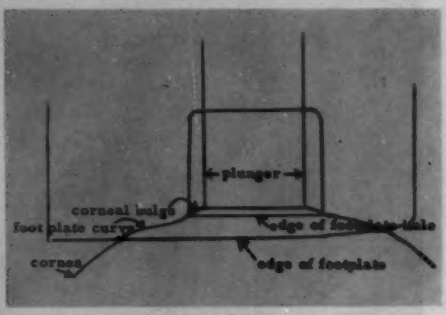


Fig. 12.—Corneal bulge in gap between footplate and plunger. Rabbit eye at P_1 equivalent to scale reading 1; 5.5 gm. plunger weight.

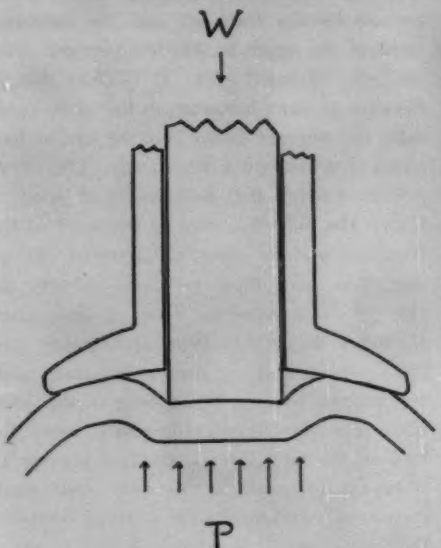


Fig. 13.—Conventional diagram of Schiøtz tonometer footplate, plunger, and corneal indentation. (Reproduced from Friedenwald.[4])

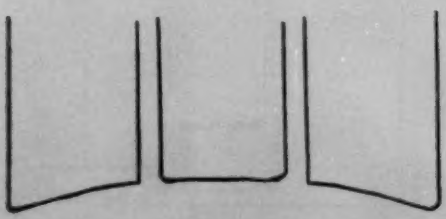


Fig. 14.—Mueller electronic Schiøtz tonometer, footplate, and plunger drawn to scale. Plunger protrusion equivalent to Scale 1.

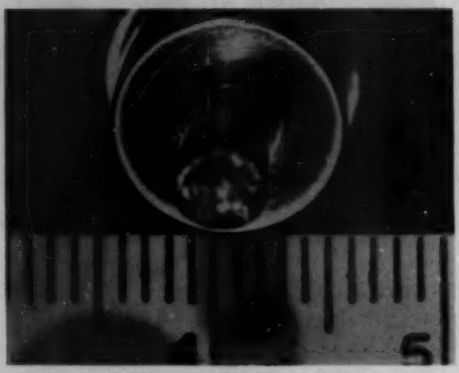


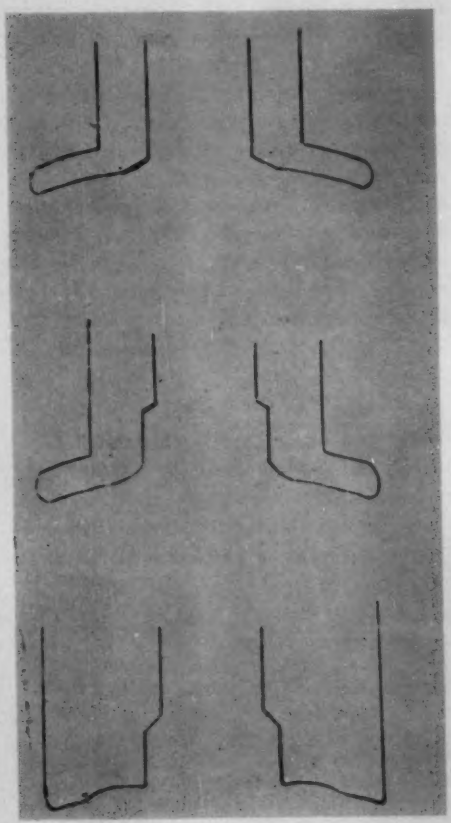
Fig. 15.—Plug gauge in place in footplate hole.

Diameter of Footplate Holes in Twenty-Five Tonometers

Type	Make	Serial No.	Diameter, Mm.
1. Gradle	American Optical	T 1193	2.79
2. Schiøtz	Jacobsen (Oslo)	25	3.05
3. Schiøtz	Sklar	G 51-2853	3.61
4. Schiøtz	Sklar	G 51-49	3.63
5. Schiøtz	Meyrowitz	5312	3.63
6. Schiøtz	Sklar	G 51-2883	3.64
7. Schiøtz	Sklar	G 51-2173	3.65
8. Schiøtz	Sklar	G 51-2081	3.65
9. Schiøtz	Sklar	G 51-3563	3.66
10. Schiøtz	Sklar	G 51-3198	3.70
11. Schiøtz	Sklar	51-2380	3.71
12. McLean	Meyrowitz	3652	3.84
13. McLean	Meyrowitz	3837	3.85
14. Schiotz	Opt. Im. Co.	1518	3.85
15. Electronic Schiøtz	Mueller	1218	3.85
16. Electronic Schiøtz	Mueller	...	3.86
17. Electronic Schiøtz	Mueller	1375	3.90
18. Electronic Schiøtz	Mueller	...	3.93
19. Electronic Schiøtz	Mueller	1308	3.93
20. Electronic Schiøtz	Mueller	1309	3.95
21. Electronic Schiøtz	Mueller	...	3.96
22. Electronic Schiøtz	Mueller	960	3.98
23. McLean	Meyrowitz	337	4.03
24. Schiøtz	Sklar	278	4.04
25. Schiøtz	Sklar	V-1617	4.05

In order to evaluate the importance of this source of error, the diameter of the footplate hole was measured with plug gauges (Fig. 15) in 25 tonometers belonging to members of the Department of Ophthalmology, Washington University School of Medicine. The Table gives the results of these measurements. It is seen that within the Schiøtz-type group the range of diameters is greater than given in the Decennial Report. It should be noted that mere measurement of the footplate hole is not sufficient to characterize the footplate. The extent of the 15 mm. radius curve is a critical feature; any variation will alter the scale reading. We have particular reference to one early Jacobsen-Schiøtz, one Sklar-Schiøtz, and one Mueller-Schiøtz tonometer which were studied especially carefully in regard to this feature. The contours of these footplates are represented schematically in Figure 16. These tonometers can be expected to give deviating readings, particularly at high pressure levels.

Fig. 16.—Schematic cross section of footplate of (*a*) Jacobsen-Schiøtz, (*b*) Sklar-Schiøtz, and (*c*) Mueller-Schiøtz tonometers. Not drawn to scale.



Recommendations

As a result of our studies we have come to the following conclusions: (1) The central hole in the tonometer footplate should be standardized. This measure should include the beveled or rounded edge of the hole. We suggest that 3.70 mm. be the maximum diameter of this zone, since this size still allows a "gap" to retard capillary creep of tears upward between barrel and plunger and since still smaller diameter holes have little effect in the range of scale readings of 3 or greater. (2) All clinical measurements of P_o and P_t with presently available tonometers at scale readings of less than 3 should be discarded unless facilities are on hand for applying suitable corrections for the given tonometer.

The tonometer used in this study had an unusually sharp plunger edge curvature, and therefore the pressure measurements are not to be construed as calibration data.

Summary

The fact has been confirmed that P_o values obtained with the 5.5 gm. and 7.5 gm. weights according to the 1955 Friedenwald tables are inconsistent below Scale 3, the 7.5 gm. weight giving the lower estimate of P_o.

In patients the size of the footplate hole influences the scale reading in the range of Scale 3 and less, the smaller hole giving the greater scale readings.

In enucleated human and rabbit eyes the scale reading corresponding to a given

manometric pressure varies with the size of the footplate hole; the smaller hole giving the greater scale readings in the range of a scale reading of 3 or less.

It was determined by direct observation through a plastic footplate that at manometric pressures corresponding to scale readings of 2 or less the cornea bulges up into the gap between footplate and plunger.

640 S. Kingshighway (10).

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The Star-Figure of the Macular Area

Histopathological Study of a Case of Angiospatic (Hypertensive) Retinopathy

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It has been our effort within the last few years to study the histology of ophthalmoscopic findings. Knowledge of the histology of such findings appears valuable, since it often helps understand their development and nature and therefore increases the significance of findings within the clinical entities.

The present paper is concerned with the histology of the retinal changes in advanced angiospastic (hypertensive, nephritic, albuminuric, arteriospastic) retinopathy. This type of retinopathy represents a very complex pathological entity of the retina with a primary vascular involvement and extensive secondary changes of the neuroectodermal tissues of the retina (neurons and glia). In this study our interest is concentrated on the histological findings which explain the ophthalmoscopic symptom of the macular star-figure. This paper represents a continuation of an earlier study on this subject which has appeared also in the ARCHIVES OF OPHTHALMOLOGY.[1]

Report of a Case

A 48-year-old Negro man was transferred to the Wayne County General Hospital on Aug. 9, 1957, from Lakeside General Hospital, Detroit, with the diagnosis of hypertensive cardiovascular disease and uremia. The patient had a history of hypertensive vascular disease since 1955 at least. He had been treated with reserpine (Serpasil), digitalization, and general supportive care. For approximately two weeks prior to this admission the patient had complained of severe abdominal pain and vomiting.

Physical examination on admission revealed a temperature of 100 F rectally, a pulse rate of 96, and respiration of the Cheyne-Stokes variety. Blood pressure was 240/160. The blood urea nitrogen was 70 mg. The skin was warm and dry. The heart was enlarged. The liver extended down 4 fingerbreadths beneath the right costal margin and was very tender. There was a trace of ankle edema. The reflexes were slightly increased throughout.

The fundi of the eyes at the time of admission exhibited a Grade III to IV angiospastic (hypertensive) retinopathy. The media were clear. The pupils were rather small and reacted to light. The ophthalmoscopic examination revealed the discs to be slightly edematous along the temporal borders. The retinal arteries were attenuated and irregular in caliber. The veins showed increased tortuosity and caliber. There was marked arteriovenous notching. Deep hard exudates were seen to be irregularly distributed all over the posterior poles of both fundi, and there were deep and superficial retinal hemorrhages. In the right eye the macular area exhibited an extensive star-figure of glistening, hard, white exudate. In the left eye there was also an incomplete macular star-figure of deep, hard exudates, but here the star-figure was not so extensive and did

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not exhibit the bright, glistening appearance of that in the right eye.

The clinical diagnoses in this patient were (1) organic heart disease, hypertensive in etiology; (2) malignant hypertension, and (3) uremia. Six days after admission the patient became very dyspneic and developed acute cardiac failure. He died on Aug. 31. At postmortem examination malignant arteriolar nephrosclerosis was found in the kidneys.

Method of Histological Examination

The eyes were injected with ammonium bromide formalin immediately after death. The posterior poles and optic nerves were removed at the postmortem examination. The posterior retinae and the optic nerves of both eyes were cut on the freezing microtome. The silver carbonate methods of del Rio Hortega[2] were used to stain these sections. The silver techniques were combined with the oil red O fat stain, which stains selectively all lipid substances bright red.

All the illustrations of this paper are unretouched photomicrographs.

Histological Findings

The flat sections of the retina of the macular area of the right eye exhibited much more advanced pathological changes than those of the left eye. It seems therefore logical to discuss in this paper the findings in the left retina first.

Figure 1 shows a low-power view of a flat section through the retina of the macula of the left eye at a relatively deep level. The nuclei of the neurons of the outer nuclear layer are seen in the center of the picture. The outer fibers of Henle's fiber layer are seen in a radial arrangement around these nuclei. The densely arranged nuclei in the periphery of Figure 1 represent the neurons of the inner nuclear layer around the foveola. Henle's fiber layer is seen to contain some large round cells, the protoplasm of which appears empty with this staining technique. The cells have a small nucleus, and some of them are also found in the inner nuclear layer. A fat stain with oil red O of parallel sections showed that the protoplasm of all these large cells stained a bright red and could therefore be considered to be filled with

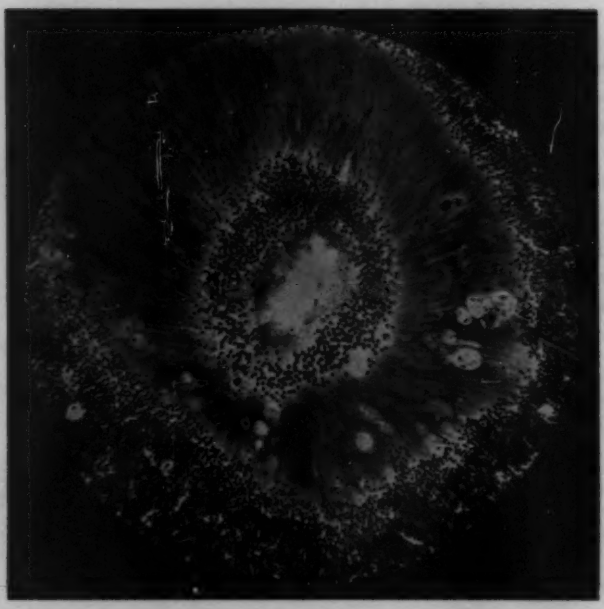

Fig. 1.—Horizontal section through the central retina of the left eye of the patient. Gitter cells are seen in the outer fibers of Henle's fiber layer (arrow). Some of these gitter cells show advanced degeneration. Hortega method; photomicrograph; × 100.

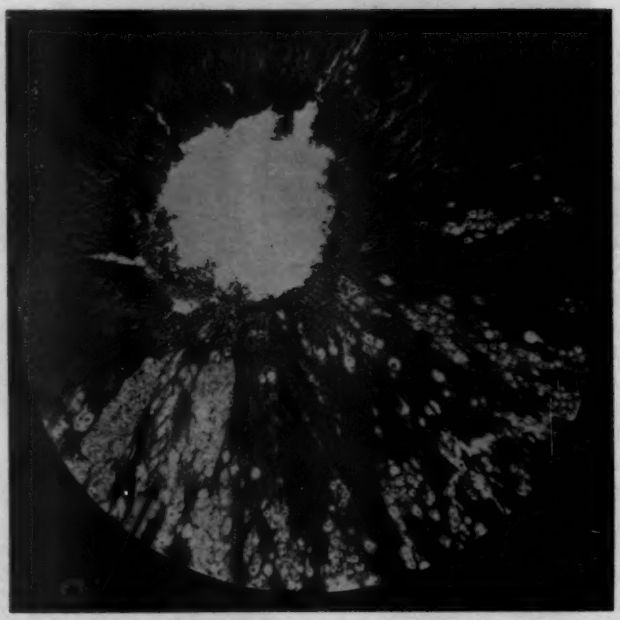

Fig. 2.—Flat section of the central retina of the left eye of the patient at a more superficial level than Figure 1. Great numbers of gitter cells are seen in Henle's fiber layer. In one area there is the confluent substance of many necrotic gitter cells (*a*). Hortega method; photomicrograph; × 100.

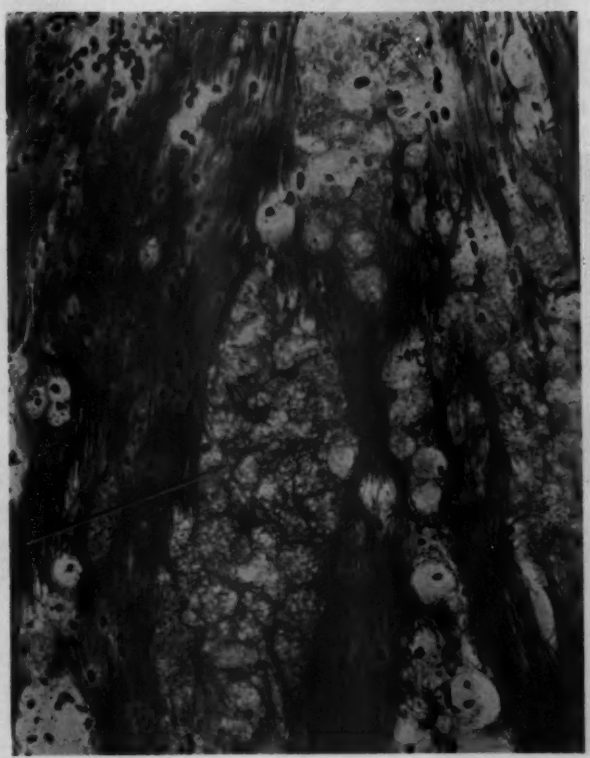

Fig. 3.—The area with the masses of free lipids in Henle's fiber layer of Figure 2 at higher power. It is clearly visible that the free lipid masses (arrow) represent the remnants of fat-filled gitter cells. Hortega method; photomicrograph; × 400.

lipids. It is clearly visible in Figure 1 that some of the lipid-filled cells have a nucleus and a distinct cellular membrane while others have no nucleus and appear degenerated.

Figure 2 represents a flat section of the central retina of the left eye of this patient which was cut parallel to that of Figure 1 at a more superficial level. The empty space in the center of the picture represents the foveola. The nuclei around this space are of the outer nuclear layer. Henle's fiber layer is clearly visible around these nuclei and exhibits a large number of the same large fat-filled cells with a small nucleus. Their protoplasm appears empty with the silver technique. The fat stain, however, showed all these calls to be completely filled with red-stained lipids. There are in Figure 2, again, many cells which exhibit a nucleus and a distinct cellular membrane. Most of the cells, however, show all stages of cellular necrosis. And there is one large area of Henle's fiber layer which contains a large mass of free lipid material (*a*). Figure 3 shows this area of Henle's fiber layer with the masses of free lipids at higher power. It is obvious that these masses of lipids represent the remnants of the fat-filled phagocytes which have become necrotic. Surviving cells of that type and similar cells in different stages of degeneration are seen around the cellular debris.

Figure 4 shows a low-power view of the innermost layers of Henle's fibers close to the foveola of the left eye of this patient. Here also we see numerous fat-laden cells of the same type as in the other Figures. One area of this Figure is seen at higher power in Figure 5. The round fat-filled cells are densely packed in the spaces of the fibers of Henle. A confluent mass of lipids is found in one area (*a*). And there are dense black-stained bodies visible within these masses of free lipids (*b*). These homogeneous black-stained bodies are composed of hyalin.

Figure 6 shows a high-power view of another area of Henle's fiber layer of the left retina of this patient. This section demonstrates that the accumulation of the fat-filled phagocytes may result in extensive damage to the elements of Henle's

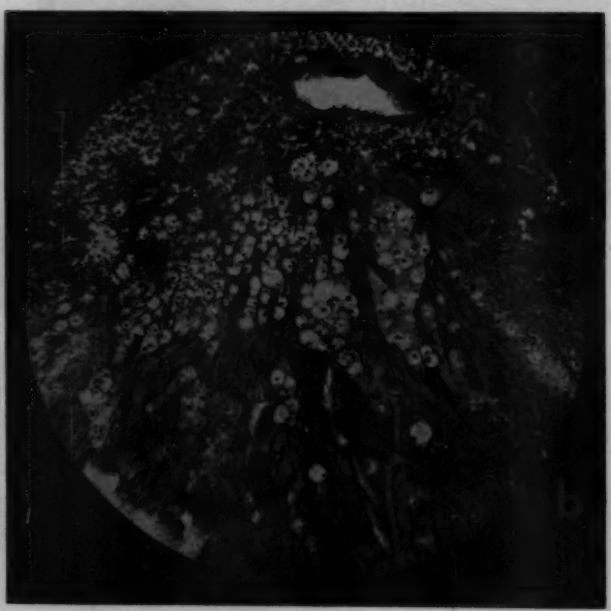

Fig. 4.—Flat section of the central retina of the left eye of the patient at the innermost level. Henle's fiber layer exhibits densely accumulated gitter cells (*a*) and large masses of lipids which contain round hyaline bodies (*b*). Hortega method; photomicrograph; ×100.

Fig. 5.—A part of Figure 4 at higher power. There are large masses of confluent lipids (*a*) and black-stained hyaline bodies (*b*) in Henle's fiber layer. There are also many gitter cells. Hortega method; photomicrograph; × 400.

fiber layer. The latter are tortuous and swollen, and many of them are interrupted.

Figure 7 shows a flat section through the central retina of the right eye of this patient. The outlines of a well-developed star-figure can clearly be recognized in this picture. The shape of the star-figure is star-like only in its central parts, where

Fig. 6. — High-power view of a part of Henle's layer in a flat section of the left eye of the patient. There is accumulation of gitter cells in this layer which show all stages of cellular degeneration (arrow). The fibers of Henle are tortuous, swollen, and interrupted. Hortega method; photomicrograph; reduced about 12% from mag. × 600.

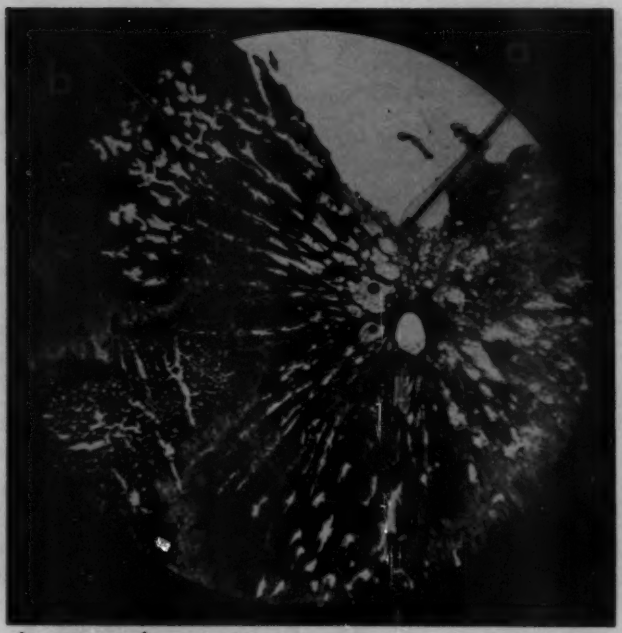

Fig. 7.—Flat section through the central retina of the right eye of the patient. The star-figure is star-shaped in its central part (*a*). It is more irregular in its periphery (*b*). A parallel section which was stained with fat stain showed all parts of this star-figure in a bright red. Hortega method; photomicrograph; × 100.

the depositions are found in the spaces of Henle's fiber layer (*a*). The deposits in the inner nuclear layer (*b*) are of a more irregular and sometimes bizarre shape. The substance of the star-figure appears unstained in Figure 1. Parallel sections after staining with oil red O, however, proved that the whole star was composed mainly of lipids and therefore stained in a bright red.

Fig. 8.—Flat section through the central retina of the right eye at a slightly more superficial layer than Figure 7. The formations of the star-figure are mainly composed of free lipid substance; but they also contain hyaline bodies and some gitter cells. Hortega method; photomicrograph; × 150.

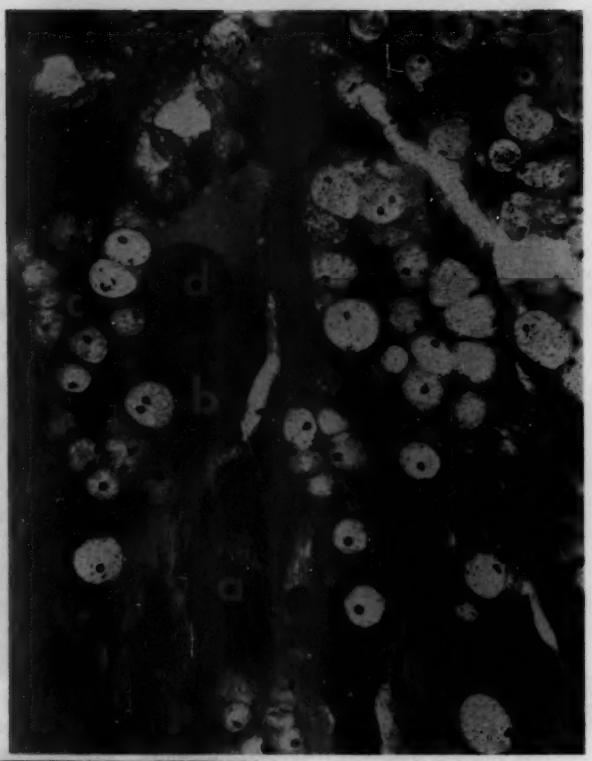

Fig. 9.—A part of the star-figure of the right eye of the patient at higher power. The fibers of Henle are compressed into small bundles (*a*). The star-figure is composed of free lipids (*b*), gitter cells (*c*), and hyaline bodies (*d*). Hortega method; photomicrograph; × 400.

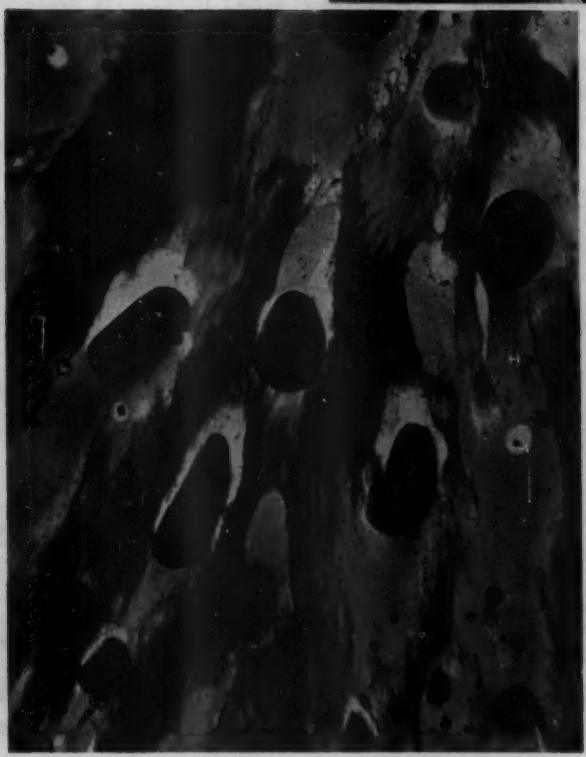

Fig. 10.—An area of the star-figure of the right eye of the patient at higher power. The free lipid substance of the star-figure contains large hyaline bodies. Hortega method; photomicrograph; × 400.

Fig. 11.—Longitudinal section of the optic papilla of the right eye of the patient. There is no histological sign of papilledema. Hortega method; photomicrograph; × 100.

Figure 8 shows the same star-figure of this right eye in a more superficial section and at slightly higher power. Again, most of the star-figure is seen to be composed of free lipid substance. However, the latter substance contains extensive islands of black-stained hyalin. There are also very few surviving phagocytes of the same type as those seen in the other pictures.

Figure 9 shows an area of a flat section of the central retina of the right eye of this patient at higher power. The fibers of Henle's layer are compressed into small bundles (*a*). Most of the photographed area is occupied by masses of free lipids (*b*), which contain fat-laden phagocytes (*c*) and hyaline bodies of different sizes (*d*). Some of these phagocytes exhibit signs of

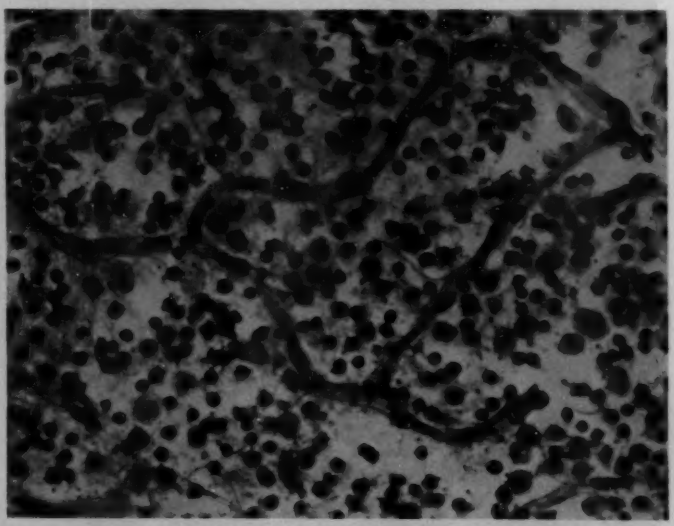

Fig. 12.—The capillary network of the inner nuclear layer in a flat section through the retina of the right eye of the patient. Hortega method; photomicrograph; reduced about 12% from mag. × 600.

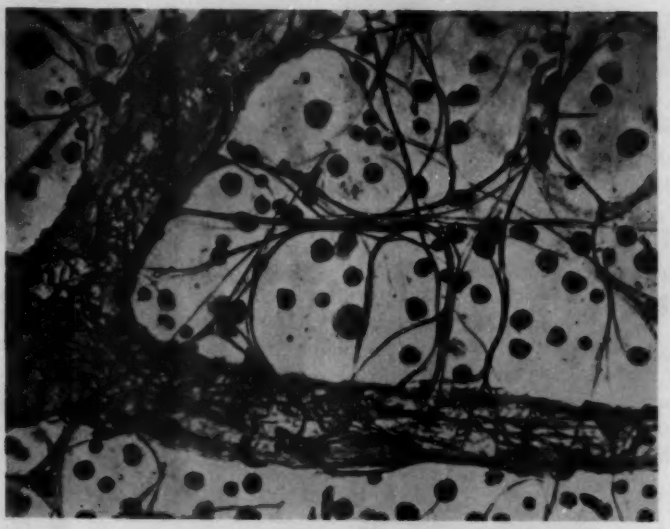

Fig. 13.—A larger blood vessel with the surrounding astroglia in the retina of the right eye of the patient. The astroglia is hypertrophic but still has its normal arrangement. Flat section; Hortega method; photomicrograph; reduced about 12% from mag. × 600.

degeneration. Figure 10 demonstrates another area of the star-figure of the right eye, which exhibits more-advanced hyalinization and fewer surviving phagocytes in the free lipid substance. Advanced destruction of Henle's fibers is also found in this Figure.

It should be mentioned that both retinae in this case histologically exhibited advanced neuronal degeneration throughout the retinal layers. There were no histological signs of papilledema (Fig. 11). It is very interesting to note that the vascular systems of both retinae exhibited only slight changes that could be seen histologically. The capillary network was virtually normal (Fig. 12) and was seen to contain continuous chains of erythrocytes in many parts of our sections. The larger blood vessels showed some sclerosis but appeared not at all occluded or severely damaged in any other way (Fig. 13). The retinal

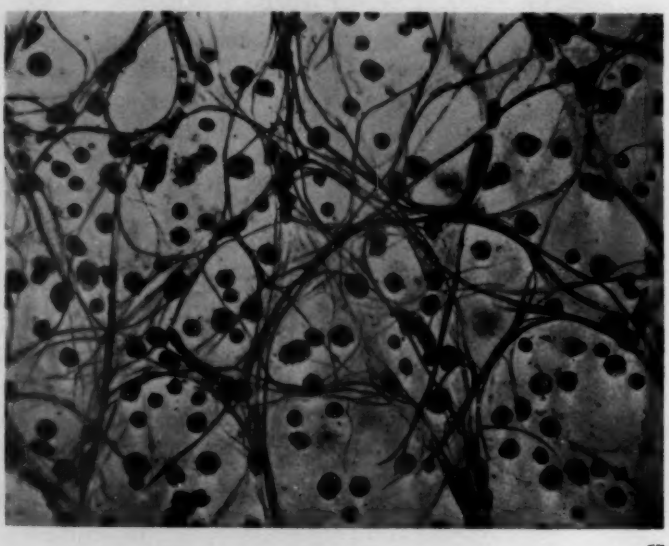

Fig. 14.—An area of the inner retina of the right eye of the patient which exhibits the hypertrophic astroglia with their long processes (glial fibers). Flat section; Hortega method; photomicrograph; reduced about 12% from mag. × 600.

astroglia exhibited an extensive hypertrophy (Figs. 13 and 14). This type of hypertrophy is usually found when there is advanced degeneration of neurons in the inner layers of the retina. The system of glial fibers and cells in this case was much denser than normal, but it still exhibited its normal arrangement and its normal relationship to the blood vessels (Figs. 13 and 14).

Comment

The present case is a very instructive one for the description and discussion of the histology of the macular star-figure in angiospastic (hypertensive) retinopathy, since the star figures in the two eyes of the patient showed two different stages of development. The star-figure in the left eye represented a rather early developmental phase of such a formation. It was mainly composed of numerous groups of round fat-filled cells which were piled up in the spaces of Henle's fiber layer and in the inner nuclear layer. These cells clearly represented microglia which had phagocytized the remnants of destroyed retinal neurons (lipids). We have discussed the nature, the origin, and the progressive changes of these cells in this condition in the earlier papers on the nature of the star-figure.[1,3] The microglia of the retina after phagocytosis of lipids have been known in the literature as "bladder cells," "ghost cells," or "spectral cells." We have stated that these cells represent typical microglial elements as seen in all parts of the central nervous system, including the optic nerve and the retina.[1,4,5] The microglia are of mesodermal origin and have been called the histiocytes of the central nervous system. Their nature and function were first discussed by del Rio Hortega,[6] and they are therefore also known as "Hortega cells." After phagocytosis of the debris of neurons the microglia represent large fat-filled elements and are then called "gitter cells" or also "granular compound corpuscles."

The gitter cells are the elements the accumulation of which in the layer of Henle's fibers and around it was found to be the histological equivalent of the ophthalmoscopical finding of the early star-figure in the left eye of the present case. Many of these gitter cells showed advanced degeneration or even complete necrosis. The lipids of great numbers of degenerated gitter cells were seen to become confluent and remained in some areas of Henle's fiber layer. Along with the development of the star-figure there was extensive degeneration of the neurons throughout the retinal layers. It is our impression that the lipids which were contained in the gitter cells and which remained in the Henle layer after necrosis of the gitter cells represented the phagocytized debris of the degenerated retinal neurons.

The star-figure in the right eye of this patient represented a much more advanced formation than that in the left eye. The star-figure in the right eye was histologically found to be composed mainly of free lipid masses which contained large bodies of hyaline substance. The fact that the lipid in this eye exhibited extensive hyalinization is considered the reason for the glistening white ophthalmoscopical appearance of the star-figure. We know from other cases with star-figures in diabetic and angiospastic retinopathy[1] that such formations may become completely hyalinized in very advanced cases and then exhibit virtually only hyalin and very little lipid substance.

The histological findings in this case and the earlier observations[1,3] indicate that the vascular involvement of the retina in angiospastic retinopathy first results in a destruction of retinal neurons. Microglia invade from the retinal blood vessels and phagocytize the lipids of the necrotic neurons. For some unknown reason these fat-laden phagocytes (gitter cells) are unable to deliver the phagocytized lipids to the blood as they do in other pathological situations with destruction of neurons.

They pile up in the retina and become necrotic. The remaining lipids form confluent masses in the retinal tissues and finally become hyalinized. Most of the gitter cells are found to pile up in the central retina. It is possible that the lack of retinal blood vessels in this area is important in explaining the localization of the star-figure.

Friedenwald [7] has pointed out that the development of the white deposits of the star-figure must be dependent upon primary changes of the small blood vessels. We were able to observe such changes in diabetic retinopathy.[1] However, it is important to emphasize that the retinal blood vessels in the present case exhibited histologically only slight pathological changes. The primary vascular pathology of the retinae in this case of angiospastic retinopathy must therefore have been of a functional nature and probably consisted of vascular spasms. The latter, of course, cannot be demonstrated in a histological slide. However, a new conception of the vascular disturbance was recently suggested by Wagener,[8] who pointed out that it is probably a spasm of the central artery of the retina alone which causes the picture of the angiospastic retinopathy. The attenuation of the retinal arteries then would be explained not by spasms but by a decrease of blood pressure in the retinal arterioles. The pathological changes in angiospastic retinopathy would have to be considered the result of poor blood supply if this theory is right. And this theory could also be used to explain the fact that the fat-filled microglia is not able to deliver the phagocytized lipids to the blood. Further studies to evaluate the nature of the vascular involvement in angiospastic retinopathy will be necessary for us to understand completely the pathological process in the retina.

Summary

The histopathology of the star-figures of the retina of a patient with a Grade III to IV angiospastic (hypertensive) retinopathy was studied with a silver staining technique. The star-figures represented different stages of the development of such formation in the two eyes. They were found to be composed of fat-filled microglia (gitter cells), of free masses of lipids, and of hyalin.

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Changes in the Tonogram During Accommodation

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Introduction

The question of whether and how the act of accommodation influences the level of the intraocular pressure has been investigated and discussed ever since the inception of scientific ophthalmology. In spite of this, the answers have remained equivocal. Yet, unequivocal answers would be helpful in deciding whether it is true, as some authors assume, that close work has a deleterious effect on the eyes of patients with early glaucoma or whether, as others think, close work by such patients should not be discouraged but, if anything, encouraged.

The question of the effect of the act of accommodation on the level of the intraocular pressure has become particularly important in recent times with the introduction of tonography for the study of the fluid exchange in the eyes. If accommodation should influence the intraocular pressure in one way or another, this could be a factor which might significantly affect the tonogram and would have to be taken into consideration.

We have undertaken to investigate the influence of accommodation on the tonogram, and the present paper is the first of a series of studies concerned with this problem. It relates to the effect of accommodation on the tonogram of young persons with "normal" eyes. It will be followed by similar studies in patients of an older age group with "normal" eyes and with glaucoma.

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Method of Investigation

1. *Instrumentation.*—It is mandatory that the eye to be examined maintain during tonometry a straight-ahead position and that the tonometer be kept vertical at all times. These precautions are necessary to avoid spurious scale readings. Therefore, since convergence forms part of the near-vision complex, an apparatus had to be designed which would not only serve the purpose of controlling and maintaining accommodation but which would also permit compensation for the convergence movements occurring with the adjustment of the eyes from distance to near fixation.

The instrument (Fig. 1) consisted essentially of a target housing and an L-shaped viewing tube. The target housing contained a 10 watt bulb which illuminated a ground-glass plate fastened to the housing in front of the bulb. The target, painted with India ink on the ground-glass plate, was a Landolt open circle; its size was such that only persons with a visual acuity of 6/6 or better could see it comfortably. The end of the target housing was made to fit by a sleeve arrangement over the long, horizontal limb of the periscopic viewing tube. The whole housing and with it the target rotated with ease around its horizontal axis. The rotation was achieved by means of a projecting knob. This knob was so placed that it pointed in the direction of the opening in the Landolt ring. Since both the knob and the target were rigidly fixed to the housing, their relationship remained constant during the rotations and the experimenter was at all times aware of the position of the opening in the Landolt ring.

The shorter vertical limb of the viewing tube carried at its open end a device into which a lens of +4.00 D. as well as lenses

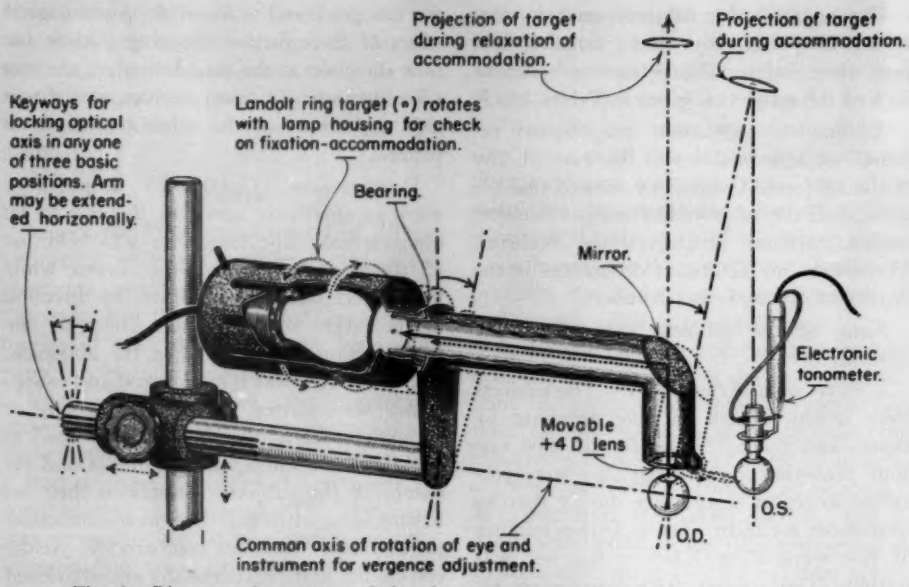
Projection of target during relaxation of accommodation.
Projection of target during accommodation.
Keyways for locking optical axis in any one of three basic positions. Arm may be extended horizontally.
Landolt ring target (•) rotates with lamp housing for check on fixation-accommodation.
Bearing.
Mirror.
Electronic tonometer.
Movable +4 D lens
O.S.
O.D.
Common axis of rotation of eye and instrument for vergence adjustment.

Fig. 1.—Diagram of apparatus designed to stimulate and maintain accommodation and to avoid vergence movements.

to correct the subject's refractive error could be fitted. At the right angle of the L-shaped tube a plane mirror was placed at a 45-degree angle, so that the rays coming from the target end would be so projected as to be in line with the central vertical axis of the vertical limb of the tube. The distance from the target plate to the open viewing end of the tube was 25 cm. Since the viewing end of the tube could be placed very close to the eye, we felt justified in considering the distance of the eye from the target to be also 25 cm. Therefore we assumed the eye of the subject to be in a condition of full relaxation if he could see the target clearly when a +4.00 D. lens and his refractive correction were placed at the viewing end of the periscope and as exercising 4 D. of accommodation when the +4.00 D. lens was removed, leaving only the lenses correcting the refractive error.

The apparatus was rigidly mounted to a horizontal rod. This rod was connected by a clamp with set screws to a vertical support which was fixed on a broad base. The whole apparatus thus could be moved easily backward or forward, moved up or down, rotated around the horizontal axis, and locked in any desired position.

A Mueller electronic tonometer was employed which had been cleared by the company and by a certified standardizing station one month before the beginning of this study. It was connected to the main current through a Raytheon voltage stabilizer. Recordings were made on a Leeds Northrup Speedomax recorder. The zero point and the calibration of the tonometer were checked before each experiment.

2. *Selection of Subjects.*—Seven subjects were selected from a total of thirteen students. The criteria for including a subject were as follows: (1) ability to see the target when the refractive error was fully corrected; this meant that the subject had a visual acuity of 6/6 or better; (2) ability to maintain the required magnitude of accommodation for four minutes without apparent effort; (3) ability to go through the test without making a mistake in indicating the direction of the target.

The ages of the subjects ranged from 18 to 25 years. Five were females, and two were males. The refractive error of each of the subjects is given in Tables 1 to 7.

A complete ophthalmic examination revealed no abnormalities in the eyes of any of the subjects. Gonioscopy showed that the eyes of all the subjects had normal chamber angles, without distinguishing features. There were no significant differences in the depths of the anterior chambers.

None of the subjects was taking any medication.

3. *Experimental Procedure.*—The subjects were instructed not to take anything by mouth and not to smoke for at least one hour preceding the test, but they were permitted to report at any time during the day convenient for them. Ten to fifteen minutes of rest were allowed before the test was started. The subject then assumed a recumbent position for tonography. The base of the apparatus was placed beneath the head end of the mattress, and the apparatus was so adjusted that the viewing end of the periscope was over one eye and as close to it as possible. Lenses correcting the refractive error were placed in the slot provided for that purpose, with or without the addition of a +4.00 D. lens, depending on the desired state of accommodation. The apparatus was then rotated and locked in such a position that the eye to be tonographed was centered and its visual axis was vertical. Throughout the study the same eye was used as the viewing eye and all tonograms were obtained from the other eye, on the supposition that accommodation is a bilateral act.

Maintenance of fixation was taken as an index for maintenance of accommodation or relaxation. To insure maintenance of fixation the target was rotated at a rate of 20 to 25 times per minute, and the subject was required to indicate with his index finger the position of the opening in the Landolt circle. Indication by finger was chosen in preference to articulation to eliminate the influence of jaw movements on the tonogram and to avoid the psychological effect of the effort of choosing a name for each direction at the rate desired. Care was taken to insure random exchange of direction and to avoid the establishment of a pattern.

Proparacaine (Ophthaine) drops were used as anesthetic agent in the eye to be tonographed. The tonometer was held for 15 to 20 seconds above the cornea while the subject started to indicate the direction of the target with the index finger of one hand resting comfortably on the abdomen. The tonometer was then lowered and tonography was started. No lid speculum or manual separation of the lids were used at any time; with adequate anesthesia and reassurance the subjects maintained their lid fissure sufficiently well open to accommodate the tonometer footplate comfortably. At the end of the first procedure the subject closed his eyes until a steady state was recovered. A steady state was considered achieved when the scale reading fell within ±0.4 scale units from that recorded at the beginning of the first tonogram and when this reading did not vary more than ±0.4 units in three determinations performed over a three-minute period. A second drop of proparacaine was then applied; the +4 D. lens was either added or removed, depending on the desired state of accommodation, and tonography was again performed. To eliminate the influence of repetition on the tonograms, the sequence of accommodation and relaxation was changed in every experiment. Experiments were at least 24 hours apart. All experiments were performed by one of us (M. F. A.).

The outlined procedure was followed throughout this study. However, at first a somewhat different method was employed. Tonography was performed in the state of relaxation or accommodation, and after a lapse of five minutes tonography was again performed in the opposite state. While this technique yielded some information, we did not feel that it was adequate, since we could not be sure that the second tonogram started

from a steady state. We, therefore, did not use the tonograms so obtained in the statistical analysis of the data, but we did take the experiences gained by the observers in the first tonograms into account in this analysis.

Results

1. *General Findings.*—A total of 48 experiments were performed on the seven observers, yielding 48 pairs of tonograms. One pair had to be discarded, because the tonometer stuck during the test, leaving 47 pairs, or 94 individual tonograms.

Visual inspection of the tonograms showed that almost without exception the tonograms taken during accommodation had a steeper slope than those taken when accommodation was relaxed. This difference was so evident that it was always possible, in comparing pairs of tonograms, to identify the tonogram taken during accommodation and the tonogram taken during relaxation without prior knowledge of which was which. As examples, seven pairs of tonograms are reproduced in Figure 2.

From the inspection the definite impression was gained that in our young experimental subjects accommodation lowered the calculated intraocular pressure or at least increased the C values of the tonograms.

To investigate the correctness of this impression, the tonograms were subjected to a thorough quantitative analysis.

Assuming that the state of accommodation had no influence on the basic suppositions on which tonographic interpretations rest, we proceeded to calculate from the tonograms values for C (facility of aqueous outflow) and for F (inflow of aqueous). We employed the tables for P_o and C which were based on the 1955 nomogram of Friedenwald, using Grant's equation for C, with the corrections for the increase in

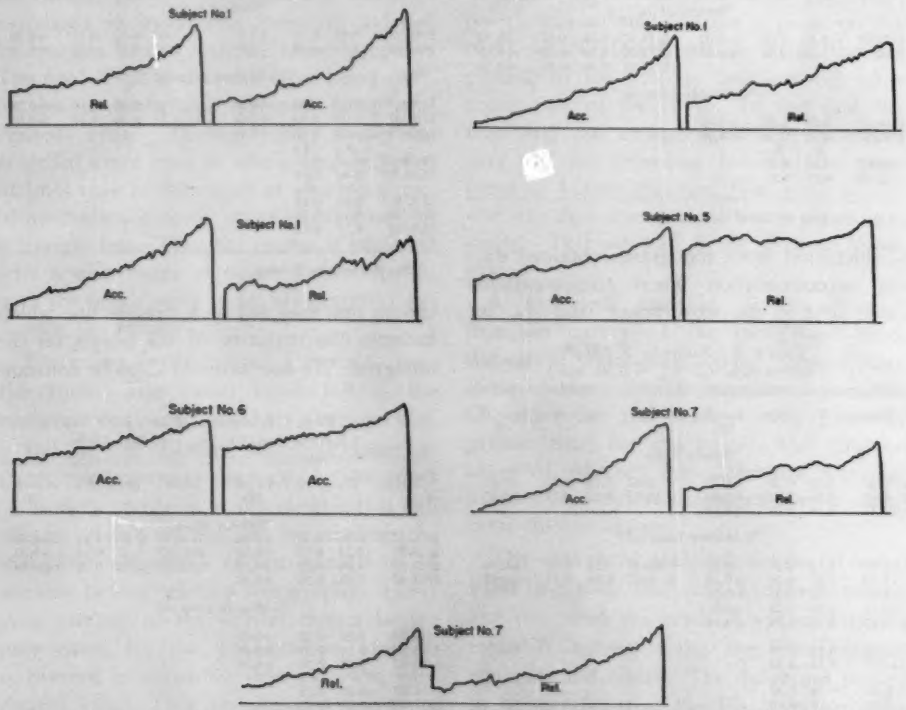

Fig. 2.—Sample tonograms. *Acc.*, tonogram taken during accommodation; *Rel.*, tonogram taken during relaxation.

TABLE 1.—*Subject 1 (F)** (Refraction O. S., +1.50 sph)

Date	A_1	R_2	A_1-R_2 (d)	Date	R_1	A_2	A_1-R_2 (d)
			"Steady State"				
2/ 7/57	0.41	0.31	+0.10	2/ 5/57	0.25	0.41	+0.16
2/ 8/57	0.74	0.24	+0.50	2/11/57	0.33	0.35	+0.02
2/14/57	0.36	0.24	+0.12	2/12/57	0.36	0.52	+0.16
2/17/57	0.70	0.25	+0.45	2/13/57	0.33	0.65	+0.32

* R_1, C values calculated from tonograms obtained during relaxation and when relaxation came first in the experiment. Sequence R_1, A_2.
R_2, C values calculated from tonograms obtained during relaxation and when relaxation came second in the experiment. Sequence A_1, R_2.
A_1, C values calculated from tonograms obtained during accommodation and when accommodation came first in the experiment. Sequence A_1, R_2.
A_2, C values calculated from tonograms obtained during accommodation and when accommodation came second in the experiment. Sequence R_1, A_2.
A_1-R_2 and A_2-R_1, difference in C values obtained from tonograms A_1, A_2, R_1, and R_2 as defined above.

episcleral venous pressure during tonography and for average ocular rigidity. The notation A_1 was used to indicate values for

TABLE 3.—*Subject 3 (F)** (Refraction O. S., −1.00 sph)

Date	R_1	A_2	A_1-R_2 (d)	Date	A_1	R_2	A_2-R_1 (d)
			"Steady State"				
1/23/57	0.45	0.43	−0.02	2/11/57	0.75	0.27	+0.48
2/13/57	0.36	0.49	+0.13	2/12/57	0.70	0.22	+0.48
				2/17/57	0.53	0.35	+0.18
			"5-Minute Interval"				
1/14/57	0.29	0.39	+0.10				
1/25/57	0.32	0.38	+0.06				
	R_1	R_2					
1/10/57	0.30	0.20					
1/12/57	0.22	0.21					

* See footnote to Table 1.

C calculated from tonograms obtained during accommodation when accommodation came first in the experiment, and A_2, for

TABLE 5.—*Subject 5 (M)** (Refraction O. S., +0.50 sph)

Date	R_1	A_2	A_1-R_2 (d)	Date	A_1	R_2	A_2-R_1 (d)
			"Steady State"				
2/ 7/57	0.12	0.25	+0.13	2/ 3/57	0.16	0.15	+0.01
2/ 8/57	0.24	0.22	−0.02	2/11/57	0.22	0.17	+0.05
2/13/57	0.18	0.39	+0.19				
			"5-Minute Interval"				
1/15/57	0.11	0.17	+0.06	1/23/57	0.22	0.13	+0.09
1/17/57	0.07	0.20	+0.13	2/ 6/57	0.20	0.13	+0.07
1/18/57	0.12	0.20	+0.08				
1/30/57	0.30	0.25	−0.05				
2/ 5/57	0.10	0.24	+0.14				
	A_1	A_2					
1/10/57	0.22	0.23					
1/11/57	0.24	0.22					
	R_1	R_2					
1/ 9/57	0.12	0.10					
1/ 9/57	0.10	0.13					

* See footnote to Table 1.

TABLE 2.—*Subject 2 (F)** (Refraction O. S., −2.50 sph)

Date	R_1	A_2	A_1-R_2 (d)	Date	A_1	R_2	A_2-R_1 (d)
			"Steady State"				
2/ 5/57	0.17	0.25	+0.08	2/ 6/57	0.27	0.25	+0.02
2/ 7/57	0.26	0.19	−0.07	2/11/57	0.30	0.21	+0.09
2/12/57	0.25	0.27	+0.02	2/14/57	0.30	0.21	+0.09
2/16/57	0.20	0.30	+0.10	2/17/57	0.36	0.13	+0.23

* See footnote to Table 1.

C values obtained when accommodation was preceded by relaxation and, therefore, came second. R_1 and R_2 indicated the corresponding C values for tonograms recorded when the eyes were relaxed. The C values for all tonograms are listed in Tables 1 to 7.

2. *Reading a Tonogram.*—In reading a tonogram the starting point and the endpoint of a tonogram are in general so

TABLE 4.—*Subject 4 (M)** (Refraction O. S., +0.50 sph)

Date	R_1	A_2	A_1-R_2 (d)	Date	A_1	R_2	A_2-R_1 (d)
			"Steady State"				
2/12/57	0.22	0.23	+0.01	2/ 7/57	0.33	0.13	+0.20
2/14/57	0.18	0.35	+0.07	2/ 8/57	0.23	0.11	+0.12
			"5-Minute Interval"				
1/ 9/57	0.21	0.42	+0.21	1/17/57	0.26	0.18	+0.08
1/10/57	0.22	0.30	+0.08	1/18/57	0.20	0.15	+0.05
1/11/57	0.20	0.31	+0.11				
	A_1	A_2					
12 /9/56	0.25	0.27					
12/12/56	0.30	0.33					
	R_1	R_2					
12/5/56	0.20	0.18					
12/6/56	0.15	0.16					
12/7/56	0.13	0.13					

* See footnote to Table 1.

chosen that they fall on a straight line which includes the majority of the points on the tonogram. If one assumes C to be constant

TABLE 6.—*Subject 6 (F)** (Refraction O. S., −1.00 sph)

Date	R_1	A_2	A_1-R_2 (d)	Date	A_1	R_2	A_2-R_1 (d)
			"Steady State"				
2/ 5/57	0.20	0.21	+0.01	1/ 4/57	0.27	0.11	+0.16
2/ 6/57	0.15	0.15	+0.00	2/11/57	0.27	0.27	+0.00
2/ 7/57	0.10	0.22	+0.11	2/12/57	0.27	0.19	+0.08
2/13/57	0.21	0.28	+0.07				
			"5-Minute Interval"				
1/18/57	0.20	0.25	+0.05				
1/23/57	0.19	0.24	+0.05				
1/30/57	0.22	0.23	+0.01				
	R_1	R_2					
1/16/57	0.20	0.23					
1/17/57	0.23	0.22					

* See footnote to Table 1.

TABLE 7.—*Subject 7 (F)**
(Refraction O. S., —3.50 sph)

Date	R_1	A_1	A_1-R_1	Date	A_1	R_1	A_1-R_1
			"Steady State"				
1/30/57	0.24	0.29	+0.05	1/31/57	0.28	0.24	+0.04
2/ 5/57	0.34	0.21	−0.13	2/ 3/57	0.35	0.26	+0.09
2/ 7/57	0.46	0.30	−0.16	2/13/57	0.47	0.21	+0.26
2/ 8/57	0.39	0.37	−0.02	2/15/57	0.33	0.33	+0.00
2/11/57	0.39	0.37	+0.08				
2/14/57	0.30	0.32	−0.02				
			"5-Minute Interval"				
1/ 4/57	0.27	0.28	+0.01	1/24/57	0.22	0.18	+0.04
1/20/57	0.30	0.30	+0.00	1/26/57	0.28	0.24	+0.04
1/23/57	0.37	0.40	+0.03				
	R_1	R_1					
1/ 6/57	0.23	0.28					
1/ 8/57	0.30	0.25					

* See footnote to Table 1.

and the volume-pressure relationship in the eye to be exponential, the tonogram would be part of an exponential curve which, being small, might justifiably be approximated to a straight line. Yet we found this procedure to be a large source of bias in clinical tonography. The tonogram records not only a change in aqueous volume but, in addition, the cardiac pulse, respiration, and transient variations in intraocular pressure induced by changes in the systemic blood pressure. The final result is thus far from being comparable to tonograms obtained from enucleated eyes. Through the tonograms recorded from eyes in situ a large number of lines may be drawn all of which approximate the tonographic curve equally well to a straight line. Thus the reader is provided with a wide range of slopes and, with this, with the opportunity to let his prejudice influence the result.

There is, furthermore, a second consideration. The initial rapid fall in the tonogram has been shown to correlate with a fall in the diastolic blood pressure as the subject's anxiety decreases.[1] The effect of anxiety and with it the rapid initial fall can be greatly minimized by holding the tonometer above the cornea for 10 to 15 seconds before starting tonography. However, anxiety of the subject cannot be the only cause for the phenomenon, since it is present to a smaller degree in the enucleated eye.[2] This phenomenon seems to be at least in part due to "creep" of an elastic membrane or to the scleral distention produced by a sudden rise in pressure. This distention induces a rapid fall in pressure, which continues until a state of equilibrium of the distention is reached.

With this background in mind, and without knowledge of which part of the tonogram was influenced by accommodation or how, a fixed system for the selection of the starting point and end-point of each tonogram was chosen. We felt that such a procedure would serve our purpose, since we were interested in a quantitative evaluation of the tonograms. The "starting point" from which P_o was determined was read from the starting point of the record, as long as it fell within ± 0.4 of a scale unit of the average of three readings taken shortly before tonography to determine a "steady state." When it did not, it was averaged with the three readings and their value was taken as the starting point. That we had to do in two tonograms. The "end-point" was calculated from a point on the curve at the fourth minute after the beginning of tonography, unless it fell on a rising part of the curve. In this case the recording was extended until the rise was over and the recording followed the same trend as before the rise. The peak of the rise was then averaged with two points in a valley. This we had to do in three tonograms.

3. *Statistical Analysis.*—It was apparent that the curves of the tonograms taken during accommodation were steeper than those obtained during relaxation, since the C values for the former were generally greater than for the latter. The question arose of whether this difference was significant or could be accounted for by variations due to chance.

The data were analyzed in several ways. First we took the data for each person and compared the mean A values with the mean R values, using the small sample equation and tables. The difference proved to be significant at the 1% level for some subjects but not for others. This method

may not have completely eliminated the influence of repetition, since we did not have equal numbers of experiments where the sequence A, R was reversed.

Our second approach was to pile up all C values for A in one column and all C values for R in another and analyze them for the differences of scores or differences in mean of A vs. mean of R. The result showed that in our data $\overline{A}$ was significantly greater than $\overline{R}$ at the 1% level, but here again the objection could be raised that the mean was biased, since not all persons had the same number of experiments.

The third approach was to take the mean values for A and the mean values for R for each person and perform an analysis of variance between $\overline{A}$ and $\overline{R}$ and between persons. When this was done, it was found that a highly significant source of variation existed between values for A and R and that there was also a highly significant difference between the subjects. However, here also it may be questioned whether the mean values were equally representative, since they were not derived from an equal number of readings in every subject.

TABLE 8.—*Data Used in Analysis of Variance* *

Subject		A_1	A_2	$\overline{A}$	R_1	R_2	$\overline{R}$
1	T_1	0.36	0.52	0.44	0.36	0.24	0.30
	T_2	0.70	0.65	0.675	0.33	0.25	0.29
2	T_1	0.36	0.30	0.33	0.20	0.13	0.165
	T_2	0.30	0.27	0.285	0.25	0.21	0.23
3	T_1	0.53	0.49	0.51	0.36	0.35	0.355
	T_2	0.70	0.43	0.565	0.45	0.22	0.335
4	T_1	0.33	0.25	0.29	0.18	0.13	0.155
	T_2	0.23	0.23	0.23	0.23	0.11	0.165
5	T_1	0.22	0.39	0.305	0.18	0.17	0.175
	T_2	0.16	0.22	0.19	0.24	0.15	0.195
6	T_1	0.27	0.28	0.275	0.21	0.27	0.24
	T_2	0.27	0.22	0.245	0.10	0.19	0.145
7	T_1	0.47	0.37	0.42	0.29	0.21	0.25
	T_2	0.33	0.32	0.325	0.30	0.33	0.315

Subject	A_1-R_1 1st Trial	A_2-R_2 2d Trial	Av. $A-R$	R_1-A_1 1st Trial	R_2-A_2 2d Trial	Av. $R-A$
1	+0.12	+0.45	+0.285	−0.16	−0.32	−0.24
2	+0.23	+0.00	+0.16	−0.10	−0.02	−0.06
3	+0.18	+0.48	+0.33	−0.13	+0.02	−0.055
4	+0.20	+0.12	+0.16	−0.07	−0.01	−0.04
5	+0.05	+0.01	+0.03	−0.21	+0.02	−0.95
6	+0.00	+0.08	+0.04	−0.07	−0.12	−0.005
7	+0.26	+0.000	+0.13	−0.08	−0.02	−0.05

* C values of four experiments on each subject are recorded. Two of these experiments were performed under sequence A_1, R_2, and two, under sequence R_1, A_2. The results are tabulated opposite T_1, first trial, and T_2, second trial. A_1, A_2, R_1, R_2 are defined in footnote to Table 1. $\overline{A}$ and $\overline{R}$, arithmetical mean. A_1-R_1 and R_1-A_1, difference in C values and the average of this difference, recorded for each subject.

TABLE 9.—*Results of Analysis of Variance* *

Source	df	SS	MS	F	F_1% Level Corrected to df
X	3	2,412	804	13.29	5.09
T	1	0.3	0.3		
S	6	4,756	793	13.11	4.01
XT	3	85	28		
XS	18	1,364	76	1.26	3.00
TS	6	402	67	1.11	4.01
XTS	18	1,089	60.5		
Total	55	10,108			

* First horizontal row: Source, source of variation; df, degrees of freedom; SS, sum of the squares; MS, mean square; F, variance ratio obtained in the study; F_1% level corrected to df, limit of variance ratio induced by variation due to chance as obtained from the tables corrected for df of the source.

First column: X, the different situations, namely accommodation when it came first, A_1; accommodation when it came second, A_2; relaxation when it came first, R_1; relaxation when it came second, R_2. Each situation is treated as being independent and different from the others. T, number of trials. S, subjects. XT, XS, TS, interaction of these sources. XTS, residual variance.

We felt, therefore, that if equal numbers of comparable readings were employed, a more satisfactory analysis of variance would be obtained. To do this we selected the last two experiments for each subject, since experience of the subject with the procedure of tonography influences the result. It could be assumed that the later tonograms would be more constant and more reliable. In choosing the tonograms, the subjects were credited with the experience gained with the earlier technique, mentioned above, in which tonography performed during accommodation or relaxation was separated from tonography in the opposite state by a five-minute interval of rest.

All data used in the analysis of variance are listed in Table 8.

The results of this statistical analysis show that two hypotheses are not tenable (Table 9).

The first: Variation in the conditions A_1, A_2, and R_1, and R_2 is due to chance. This hypothesis had to be rejected at the 1% level, since $F_{1\%}$ with 3 df (degrees of freedom) was 5.09 and $F_x=13.29$. The difference was highly significant.

The second: The differences in Subjects 1 to 7 were due to chance. This hypothesis had to be rejected at the 1% level, since $F_{1\%}$ with 6 df=4.01 and $F_x=13.11$. The differences between the subjects were highly significant.

TABLE 10.—*Analysis of Variance Between A_1 and A_2**

$\overline{A}_1$=37.36	t=0.76
$\overline{A}_2$=35.14	df=14
S. D. $\overline{A}_1-\overline{A}_2$=8.643	t_1%=2.98
S. D. $\overline{A}_1-\overline{A}_2$=2.04	

* $\overline{A}_1$, mean of C values under situation A_1, multiplied by 100 for simplicity; $\overline{A}_2$, mean of C values under situation A_2, multiplied by 100. S. D.^{2} $\overline{A}_1-\overline{A}_2$, square of the standard deviation of the difference between the means; S. D., standard deviation of the difference between the means; t, ratio obtained from data; t_1%, limit of ratio at 1% level of confidence and degrees of freedom of the source due to chance variation as obtained from "Student's" tables.

Wherein lay the significant variation between treatments? Analysis of A_1 vs. A_2 (Table 10) revealed that there was no significant difference at the 1% level between the two. The same could be said for R_1 and R_2 (Table 11): At the 1% level there was no significant difference.

But when we analyzed the difference between $\overline{A}=\frac{A_1+A_2}{2}$ and $\overline{R}=\frac{R_1+R_2}{2}$ (Table 12), this difference was found to be highly significant: t_1% for 28 df=2.76 and $t(\overline{A}-\overline{R})$=6.01.

Thus, the significant difference obtained in the tonograms in the two experimental conditions was created by an intrinsic difference in the accommodated and relaxed state and not by repetition.

The analysis of the F values yielded the same results as that of the C values. This was to be expected, since P_o was not significantly different for the two states of accommodation and relaxation.

TABLE 12.—*Analysis of Variance Between $\overline{A}$ and $\overline{R}$**

$\overline{A}$=30.25
$\overline{R}$=23.75
S. D.^{2} $\overline{A}-\overline{R}$=MSE $\left(\frac{1+1}{n\overline{A}\ n\overline{R}}\right)$=60.5$\left(\frac{1}{14}\right)$=4.32143
S. D. $\overline{A}-\overline{R}$=2.08
t $\overline{A}-\overline{R}$=12.5/2.08=6.01
df=28
t_1%=2.76

* $\overline{A}$, mean of all C values obtained during accommodation, regardless of whether it came first or second: $\frac{\overline{A_1+A_2}}{2}$; $\overline{R}$, mean of all C values obtained during relaxation, regardless of whether it came first or second: $\frac{\overline{R_1+R_2}}{2}$.

TABLE 11.—*Analysis of Variance Between R_1 and R_2**

$\overline{R}_1$=26.36	df=14
$\overline{R}_2$=21.14	t_1%=2.62
S. D. $\overline{R}_1-\overline{R}_2$=2.94	t_5%=2.14
t=1.78	t_{10}%=1.76

* $\overline{R}_1$, mean C values from tonograms during relaxation, when relaxation came first; R_2, mean C values from tonograms during relaxation, when relaxation came second; t_1%, t_5%, t_{10}%, corrected t-values obtained from "Student's" table for degree of freedom of the source and for different levels of confidence.

Comment

The data presented in this paper and their statistical analysis give unequivocal evidence that in young normal subjects the C values of the tonograms are greater when the eye is accommodating than when it is relaxed.

In trying to explain these findings, the following mechanisms must be considered, each of which, either singly or in combination, could cause an increase of the steepness of the tonogram during accommodation: (1) an increase in the facility of outflow of aqueous during accommodation (2) an inhibition of aqueous formation during accommodation (3) an increase in ocular rigidity during accommodation, producing steeper tonometric curves which would not represent real changes either in facility of outflow or in aqueous formation (4) a reduction in the volume of the ocular contents during accommodation (5) changes in intraocular pressure reflecting changes in systemic blood pressure induced by the accommodative effort.

The procedure used in this study does not provide the kind of information required to enable one to tell whether the steeper tonograms obtained during accommodation are due to an increase in facility

TABLE 13.—*Analysis of Variance for Order Effect**

$\overline{A_1+R_1}$=31.86	t_1%=2.76
$\overline{A_2+R_2}$=28.14	t_5%=2.05
t=1.8	t_{10}%=1.70
df=28	

* $\overline{A_1+R_1}$, mean of all C values obtained during accommodation and during relaxation when these situations came first in the experiment; $\overline{A_2+R_2}$, mean of all C values obtained during relaxation and during accommodation when these situations came second in the experiment.

of outflow or to an inhibition of aqueous formation. Either one, occurring during accommodation, would have the same effect on the tonogram. If an inhibition of aqueous formation were operative, then the eye during accommodation would no longer be in a steady state. Hence the C values, while serving adequately as a measure of the slope of the tonograms, would, however, not carry the same meaning as they do in tonography under a steady state, where they represent an estimate of the facility of aqueous outflow.

The ocular rigidity factor could also produce an increase in the slope of the tonogram. The steeper slope during accommodation would then be an expression of the fact that a certain volume change produces a different pressure change when the eye is accommodating than when it is relaxed. While ocular rigidity had been found to be constant for a given eye, thus making it possible for identation tonometry to promise to give a valid measure of intraocular pressure rather than of tension, more-recent studies[4,5] show that this assumption needs to be modified. Ocular rigidity, as defined by Friedenwald, does change with pressure. We have found[2] that certain extraocular, orbital factors do alter the ocular rigidity significantly when it is determined by paired readings with 5 gm. and 10 gm. weights and the results are evaluated with the 1954 tables of Friedenwald. If a change in ocular rigidity should occur during accommodation as a result of the altered tonus of the extraocular muscles, then this would produce an increase in the slope of the tonographic curve which would not be due to an actual alteration in the facility of outflow. An attempt was made to evaluate the factor of ocular rigidity by taking paired readings during accommodation and relaxation. The results were so widely scattered, and often so meaningless, as to convince us that this method was unsuitable for our purpose. However, one could reason that if ocular rigidity did increase during accommodation one should expect a change in the initial scale reading, indicating an increase in pressure at the beginning of accommodation. Since we found no significant difference in P_o during accommodation and during relaxation, it is unlikely that there was a change in ocular rigidity.

Furthermore, tonometry performed at the beginning and at the end of four minutes of accommodation revealed a significant reduction in calculated intraocular pressure. The mean reduction in the seven subjects was 1, 3, 1, 5, 6, 5, and 3 mm. Hg, respectively. If these reductions did not represent an actual decrease in intraocular pressure, then they would have had to represent a decrease rather than an increase in ocular rigidity. Hence, the increase in the slope of the tonograms during accommodation could not be explained by a change in ocular rigidity.

A reduction in volume of the ocular contents—whether this be a reduction in intraocular blood volume or in intraocular muscle volume—could account for the results obtained. At present we have no information about the behavior of the blood volume during accommodation. But work with stimulation of the autonomic nervous system in the enucleated eye[6] shows that the change in volume of the ciliary muscle during its contraction produces a slight rise rather than a reduction in intraocular pressure. Hence, this effect of the contraction of the ciliary muscle would tend to minimize the total lowering of the pressure encountered during accommodation and could not account for it.

Changes in systemic blood pressure during accommodation could cause a change in the tonogram. We did not measure the systemic blood pressure during the tests, but if a change had occurred this should have expressed itself in the initial readings or in the quality of the tonographic curves, neither of which was encountered in this study.

An increase in the facility of outflow or a reduction in aqueous formation or in intraocular blood volume are the mecha-

nisms which best account for decrease in intraocular pressure during accommodation in our subjects. Our data do not permit us to decide by which one of these mechanisms—singly or in combination—the effect was achieved. All that we can infer with confidence from our data is that in young subjects with normal eyes the intraocular pressure is lowered during accommodation, as evidenced by the increase in the C values of the tonograms.

This in itself is an important observation and will gain in importance in relation to the proposed studies in persons in the older age group and with glaucoma. But it also has significant implications with regard to the technique of clinical tonography.

Our findings indicate that the fixation distance and more particularly changes in the fixation distance during tonography may influence the tonogram obtained. While our data refer only to young persons, for whom clinical tonography is rarely done, it would seem justified to extend them at least tentatively also to older age groups.

Maintenance of the fixation distance may be a minor point in tonography as routinely performed by the method of Grant, since here the patient is in a recumbent position and does presumably fixate a relatively distant object. It may be of major importance if tonometry is done with the applanation tonometer of Goldmann. In this procedure the patient is placed at the slit lamp and fixates with one eye on the fixation light provided with the slit lamp while the other eye is being measured. One might think that the fixation light is not a good stimulus to accommodation and that the error induced might, therefore, be negligible. We did not have an applanation tonometer at our disposal to verify the influence of the fixation light on tonometric readings by this method, but we did place two of our subjects in front of a Haag-Strat slit lamp and asked them to fixate the fixation light steadily for four minutes. Somewhat to our surprise, we found that after they did this the scale readings of the tonometer in the two subjects had dropped from 4 to 5 and from 4 to 6, respectively. It must, therefore, be assumed that the stimulus exerted by the fixation light was sufficient to induce enough accommodation to lower the intraocular pressure by a significant amount.

Summary

This paper reports the results of the influence of accommodation on the tonograms of seven young subjects with normal eyes.

It was found that in these subjects the C values of the tonograms were greater when the eye was accommodating than when it was relaxed. A careful statistical study showed that the difference obtained in the two experimental conditions was significant and was created by an intrinsic difference between the accommodated and the relaxed state and not by repetition.

The possible mechanisms by which the intraocular pressure may be lowered during accommodation are discussed. Increase in facility of outflow or a reduction in aqueous formation or in intraocular blood volume are the mechanisms which best account for this lowering. However, the data obtained do not permit one to decide by which one of these mechanisms—singly or combined—the effect is achieved.

The importance of the findings of this study for the technique of tonography and tonometry is pointed out.

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The Effect of Chlorothiazide (Diuril) on the Intraocular Pressure of Animals and Humans

A Preliminary Report

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An oral diuretic, chlorothiazide (6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide) (Diuril) has been found to be an effective hypotensive agent in cases of arterial hypertension as well as a potent diuretic.[1-5]

Initially this agent was believed to be a strong inhibitor of carbonic anhydrase in vitro. For this reason the present studies were undertaken to determine its potential ocular hypotensive action.

Recent reports have demonstrated that the renal action of chlorothiazide more closely resembles that of mercurial diuretics than that of carbonic anhydrase inhibitors.[1-5]

Experimental Animals

Twelve normal pigmented rabbits weighing between 5 and 7 lb. were used to study the effect of intravenously administered chlorothiazide on the intraocular pressure.

After topical anesthesia with 0.5% tetracaine (Pontocaine) the initial intraocular pressure was determined. Immediately afterward, chlorothiazide, 30 mg. per kilogram of body weight, was given intravenously. Tonometric readings were then obtained at 30-minute intervals for 3 hours.

No significant change in the intraocular pressure was noted during the three hours of observation.

The drug was well tolerated by all the animals.

Wills Eye Hospital.

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Humans

Nonglaucomatous Eyes.—The effect of a single oral dose of chlorothiazide was studied in 25 patients with nonglaucomatous eyes. In all cases comparison of the intraocular pressure before and after administration of the drug was the prime interest. After determination of the initial tension, 500 mg. of chlorothiazide was given orally, and tonometric readings were repeated at hourly intervals for three hours, with use of a Schiøtz tonometer.

No significant change in the intraocular pressure that could be attributed to this drug was observed. The results obtained are similar to those found in an equal number of patients that had not received chlorothiazide (Table).

Glaucomatous Eyes.—The effect of a single oral dose of chlorothiazide was studied in 25 cases of various types of glaucoma. In all patients miotic medication was discontinued the night preceding the test. No significant change was observed in the intraocular pressure following the administration of the drug in doses of 250, 500, and 750 mg. After the administration of 500 and 750 mg. of chlorothiazide the changes noted were similar to those obtained in the same patients when no drug was given (Table).

The effect of repeated daily doses of chlorothiazide was also studied in 20 patients with various types of glaucoma for periods of time varying from two to six weeks. The drug was given three times daily. In most cases the total daily dose used was 750 or 1500 mg.

Average Hourly Change in Intraocular Pressure in Nonglaucomatous and Glaucomatous Eyes When No Drug Was Given (Controls) and After Chlorothiazide by Mouth

Diagnosis	Patients, No.	Dosage, Mg.	Av. P_1*	Av. P_2*	Av. P_3*
Nonglaucomatous	25	None, controls	−0.4	−0.8	−0.7
Nonglaucomatous	25	500	−0.3	−0.5	−0.5
Glaucomatous	20	None, controls	+0.4	+0.8	+1.3
Glaucomatous	20	500	+0.2	+0.1	+1.3
Glaucomatous	10	750	+0.9	+1.3	+1.5

* Av. P_1, P_2, P_3 indicates average hourly change in intraocular pressure in millimeters of mercury at the end of one, two, and three hours.

No significant lowering of the intraocular pressure was observed in any of the patients studied.

Effect of Chlorothiazide on Aqueous Humor Dynamics

Comparison of tonographic tracings obtained in normal and glaucomatous patients before and after administration of chlorothiazide revealed that this drug did not have any obvious effect on the aqueous humor dynamics.

The oral administration of chlorothiazide in the dosages mentioned above was not associated with any undesirable side-effects.

Summary

Systemically administered chlorothiazide (Diuril), a potent diuretic and effective hypotensive agent in arterial hypertension, had no significant influence on the intraocular pressure of rabbit or human eyes in the dosage employed.

The drug used in this experiment was supplied by Merck Sharp & Dohme, Division of Merck & Co., Inc., Philadelphia.

Wills Eye Hospital, 1601 Spring Garden St. (30).

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Intraocular Tumors

I. Bilateral Hemangioma of the Choroid

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During the past 10 years the Retina Service of the Massachusetts Eye and Ear Infirmary has attempted to serve the difficult function of helping not only with the diagnosis and treatment of retinal detachments but also with that of other fundus conditions. This series of articles is intended to describe and discuss salient findings and results of therapy in a number of cases of intraocular tumors. The first report concerns a patient with bilateral hemangioma of the choroid who was seen by many excellent ophthalmologists over a period of years before the correct diagnosis was finally made. The tentative diagnoses proposed by these ophthalmologists serve to emphasize the different possibilities which must be considered in this condition. Hemangioma of the choroid is difficult to recognize prior to enucleation, and a review of this patient's history should make us more aware of this condition and perhaps avoid needless enucleation and misdirected therapy. This case also is dramatic because, as far as is known to us, it is the first time that a bilateral hemangioma was ever diagnosed by biopsy in the living eye and treated on the basis of this biopsy without enucleation.

Case Description

A 55-year-old woman, a textile designer by profession, was admitted to the Massachusetts Eye and Ear Infirmary in March, 1954, for the treatment of bilateral retinal detachments. The following were important points in her past history. In 1924 the patient's mother was found to have a positive Wassermann reaction, and she herself also had a positive serologic reaction, for which she was given adequate arsenical treatment. In 1939 she had pulmonary tuberculosis which was treated with pneumothorax and bed rest for one year. She suffered a reactivation of her pulmonary tuberculosis in 1950 and received streptomycin; some time after this treatment the lesion was healed. In 1948 a nonmalignant tumor was removed from her left breast.

As far as the present illness is concerned, the patient had been seen since 1941 by optometrists and many outstanding opthalmologists on an average of every 6 to 12 months because of dissatisfatcion with her visual acuity. Even though she needed a progressive increase in the strength of her hyperopic correction during this period, records which we have been able to obtain show that as late as 1950 her visual acuity could be corrected to R. E. 20/30 and L. E. 20/25. Her refraction history since 1932 is presented in the Table. The glasses as noted were prescribed by 12 different optometrists and ophthalmologists.

In 1950 the patient became more dissatisfied with her vision, and in May, 1952, she was seriously troubled by fluttering spots and increasing difficulty in seeing with the right eye. In July, 1952, her vision was R. E. 20/200 and L. E. 20/25, with a correction of +11.00 sphere for each eye. The loss of central vision in the right eye was unexplained, but some

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Refractive Error and Visual Acuity

	Right Eye		Left Eye	
Date	Refraction	Corrected Vision	Refraction	Corrected Vision
11/1932	+ 2.25+0.25 90°	--	+ 0.25	--
5/1941	+ 6.00+1.00 180°	20/29	+ 2.00+0.50 180°	20/22
1/1943	+ 6.75+0.75 180°	20/22	+ 2.75+0.75 180°	20/22
9/1943	+ 7.50+0.75 180°	20/22	+ 3.25+0.75 180°	20/22
10/1944	+ 8.00+0.75 180°	20/30	+ 3.75+0.50 180°	20/30
5/1945	+ 8.50+0.75 180°	20/30	+ 4.50+0.50 180°	20/30
11/1946	+10.00+0.50 180°	20/30	+ 6.00+0.50 180°	20/20
7/1948	+ 9.50+1.00 150°	20/30	+ 6.00+0.75 45°	20/20
6/1949	+10.00+0.75 180°	20/40	+ 8.00+0.50 20°	20/30
7/1950	+ 9.50+0.75 180°	20/30	+ 8.00+0.50 180°	20/25
11/1950	+ 9.75+0.75 180°	--	+ 8.75+0.75 180°	--
2/1952	+ 9.75+0.75 180°	--	+ 9.75+0.50 180°	--
5/1952	+ 9.75+0.75 180°	--	+10.50	--
6/1952	+ 9.75+0.75 180°	--	+11.00+0.75 5°	--
7/1952	+11.00	20/200	+11.00	20/25
1/1953	--	--	--	20/70
2/1953	--	20/300	--	20/200
3/1954	+11.00	20/400	--	H. M. 2 ft.
11/1954	+ 5.50+0.75 180°	20/200	+ 7.50	C. F. 1 ft.
10/1955	+ 4.50+1.50 180°	25/200	--	--
11/1956	+ 4.50+1.50 180°	20/200	--	L. P.
3/1957	+ 4.50+1.50 180°	20/200	--	No L. P.

macular anomaly was suspected. Examination of the left eye, which had a vision of 20/25, revealed the presence of a lower retinal detachment. As no retinal breaks were detected, the detached area was treated with diathermy, but attempts to drain the subretinal fluid were unsuccessful. Although the retina appeared to reattach shortly after operation, vision in the left eye slowly decreased to 20/70 six months postoperatively. A definite difference was then noted in the elevation of the macular region as compared with the rest of the retina. This elevation was ascribed to an exudative type of retinal detachment, which was also held responsible for the progressive hyperopia. The retinal vessels and the transparency of the retina were reported to be normal. About eight months after operation on the left eye, corrected visual acuity on this side deteriorated to 20/200. The patient was then seen by two consultants who felt that a choroidal mass was present at the posterior pole of each eye. The nature of the masses was not determined, but because of the patient's history the following possibilities were listed: malignancy (either primary or metastatic), tuberculoma, and syphilitic granuloma. A repeated treatment with streptomycin was instituted, and it was stated that it caused a reduction in the size of the choroidal tumors. On discharge corrected vision was 20/200 in each eye.

Fifteen months after the retinopexy on the left eye, another ophthalmologist believed that the patient had an inflammation of this eye and treated her with corticotropin (ACTH). The eye condition was said to improve somewhat, but shortly thereafter an inferior retinal detachment was again found in the left eye. No retinal breaks were seen. In December, 1953, eighteen months after the first operation, a second diathermy operation was performed for detachment of the left retina. Two weeks later another ophthalmologist found bilateral retinal detachments, "probably on an exudative inflammatory basis." The patient was then seen by an otorhinolaryngologist, who found tonsil tags and a chronic postnasal drip. Although she had had a tonsillectomy a number of years previously, this operation was repeated, and tonsil tags were removed as a possible focus of infection. Complete urinalysis and blood cell count were essentially negative.

When first seen at the Retina Service of the Massachusetts Eye and Ear Infirmary, in March, 1954, the patient's best vision with correction and pinhole glasses was R. E. 20/300 and L. E. hand movements at 3 ft. She had been wearing pinhole glasses since her last diathermy operation four months previously, and so she could not tell how much her vision had changed. Fundus examination (Fig. 1) revealed that the retina of the right eye was flatly detached except for the upper third, which was in place. The detachment was limited above by a narrow demarcation line. In the detached portion of the peripheral retina many small retinal vessels were obliterated. At the posterior pole there was a salmon-colored choroidal mass which was not adherent to the detached retina. The mass was roughly circular and had a diameter of 6 to 7 discs. No retinal breaks were found. The left eye showed a total retinal detachment (Fig. 1), with marked

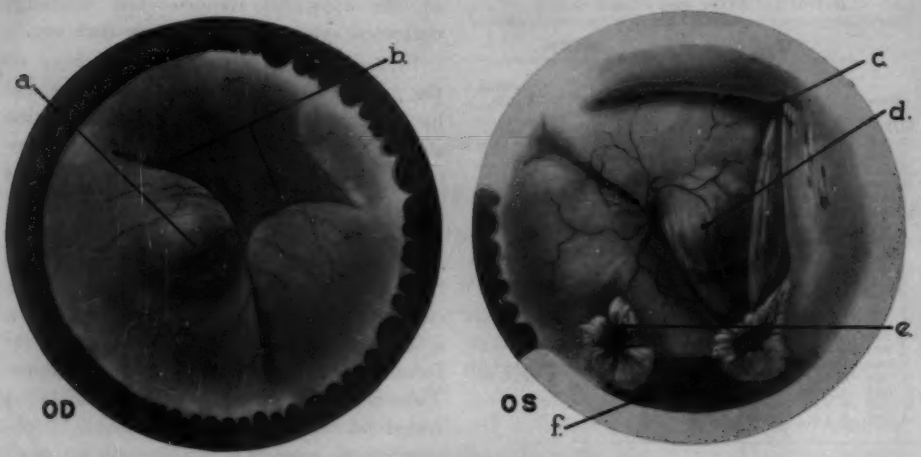

Fig. 1.—Sketch of both fundi, made in March, 1954. In the right eye a subtotal flat retinal detachment covers a salmon-colored choroidal tumor (*a*), without adhering to it; the retinal detachment is limited above by a slightly pigmented demarcation line (*b*); many of the peripheral retinal vessels are obliterated in the area of the detachment. No retinal breaks are found. In the left eye a total retinal detachment with fixed retinal folds is present. Scars of previous diathermy applications are visible temporally (*c*). A large choroidal mass is found at the posterior pole, under the detached retina (*d*). Two perforations (*e*), located at 5 and 7 o'clock, have caused extensive proliferation of newly formed tissue into the vitreous cavity. A vitreous hemorrhage (*f*) obscures the lower portion of the fundus. The ora serrata is visible only nasally, because of marked vitreous haze in the periphery.

fixed folds. The scars of two previous diathermy operations were clearly visible temporally. At 5 and 7 o'clock, where two perforations had been made for the release of subretinal fluid, there was extensive tissue proliferation, with new vessels radiating from the point of perforation into the vitreous cavity. A choroidal mass, similar to that seen in the right eye, was visible at the posterior pole; it was, however, much larger and measured about 10 disc diameters. No retinal breaks were found.

It is of interest that the choroidal masses located behind the detached retinas could only be seen with the strong light and stereopsis of an indirect ophthalmoscope. None of the four ophthalmologists called in consultation at the Massachusetts Eye and Ear Infirmary could see these tumors with a direct ophthalmoscope. The patient's skin showed no nevi in any location. The idea of syphilitic eye lesions was discarded by a consultant dermatologist; a phthisiologist thought the choroidal tumors might be tuberculomas, and after a careful general examination an internist found no signs of metastatic carcinoma. Blood, urine, and spinal fluid showed negative cytological, chemical, and serological results. X-rays of the skull and orbits were negative, no calcifications being detected in either location. Lung x-rays were consistent with the patient's past history of tuberculosis. She was advised to have the left eye enucleated so that a diagnosis could be made, with hopes of saving the right eye, which appeared least affected. As this advice was rejected, it was decided to perform a biopsy, under general anesthesia, of the tumor in the left eye. This operation was done in March, 1954, twenty-two months after the first retinopexy on the same eye.

After exposure of the sclera, the lateral rectus, inferior rectus, and inferior oblique muscles were detached. The temporal edge of the tumor was localized by means of a

binocular indirect ophthalmoscope and a surface electrode. This method of localization will be described in further detail in a subsequent article. Transillumination revealed a sharp outline, with no transmission of light. A V-shaped incision was made in the sclera over the tumor. The apex of the V was located 22 mm. from the limbus, one branch of the incision running above and the other below the optic nerve. Three preplaced 0000 nonabsorbable surgical (silk) sutures were inserted through the lips of the scleral incision before the choroid was bared. After elevation of the flap of sclera, the tumor was visualized as an integral part of the choroid and indistinguishable from it grossly. Three separate pieces of tissue, each measuring approximately 1.5×2×3 mm., were excised with a Bard-Parker blade and scissors. At excision it was felt that the tumor had a leathery consistency. A moderate amount of bleeding ensued externally, but no vitreous presented. Ophthalmoscopically there was no change in the appearance of the tumor except for a few small hemorrhages in the region of the excision. The scleral sutures were tied. Subretinal fluid was removed in the lower temporal quadrant, away from the location of the tumor, by the method usually employed for this purpose at the Retina Service.[42] About 1 cc. of viscid xanthochromic fluid was obtained and was injected into a guinea pig. It failed to produce either tuberculosis or other inflammatory lesions. The extraocular muscles were reattached; the conjunctival wound was closed, and a pressure dressing was applied. Postoperatively there was a small subretinal hemorrhage in the region of the biopsy, and the choroidal tumor was still visible. The retinal detachment settled gradually until, two months later, the retina was almost completely reattached, but the disc appeared very pale.

The microscopic specimens were examined by Dr. Parker Heath, who reported a diagnosis of choroidal hemangioma. The tumor was composed of blood vessels fairly uniform in size; there were some collections of endothelial cells without blood channel formation. This diagnosis was confirmed by several other distinguished eye pathologists.

Eight months after the biopsy, vision with correction had improved from hand movements at 2 ft. to counting fingers at 1 ft., and the visual field had increased markedly. The refractive error had decreased from +11.00 D. to +7.50 D. Twenty-eight months after the biopsy an equatorial fixed retinal fold appeared in the inferior half of the fundus where newly formed tissue had been present as a result of perforations of the globe for unsuccessful attempts at releasing the subretinal fluid. This equatorial fold gradually extended all around the globe. From its crest an equatorial membrane was visible and stretched across the vitreous cavity. In the course of the following eight months the retina redetached completely, many of the retinal vessels became obliterated, the vitreous cavity became hazy with cellular proliferation from below, and the patient lost light perception with this eye. The contours of the choroidal tumor could still be seen, and there was no marked change in its size or color. This was three years after the biopsy and nearly five years after the first retinopexy.

Because of the similarity in the appearance of the lesion beneath the right macula, the parallel progressive hyperopia over a period of many years, and the existence of a retinal detachment without retinal breaks, it was inferred that the lesion in the right eye was also a hemangioma of the choroid. Therefore, a few days after operation on the left eye, the right eye was operated upon and the macular tumor treated with diathermy.

After incision through the conjunctiva and Tenon's capsule, the lateral rectus, inferior rectus, and inferior oblique muscles were detached to expose the posterior pole. As light was found not to be trans-

mitted through the tumor, a transilluminating electrode was used to mark its limits during observation with a binocular indirect ophthalmoscope. A black silk suture was passed through the superficial layers of the sclera as a landmark for the temporal border of the tumor. A needle electrode, 3 mm. long, was inserted into the tumor, with diathermy current of moderate intensity being used for 10 seconds at each application. Seven such applications were spaced evenly over the tumor. During some of them a few gas bubbles appeared under the retina. Then 13 applications of two to three seconds' duration were evenly interspersed throughout the tumor, with use of the same electrode. No perforation of the retina was caused by any of these diathermy applications, which were all done under constant ophthalmoscopic control. An attempt was made to release subretinal fluid in the inferior temporal quadrant, 17 mm. from the limbus, where a fairly large balloon was present preoperatively. As the horizontal position of the patient had caused the fluid to shift from the lower portion of the fundus to the posterior pole, no subretinal fluid was obtained. Postoperatively the retina settled gradually, and, after seven months, no detachment could be detected. Central vision with correction had improved from 20/400 to 20/200, and the visual field became larger. The refractive error decreased from +11.00 D. sphere to +4.50 D. sphere. The tumor itself was still visible, but it appeared flatter and showed pigmented scars in its center and along its temporal border. The nasal edge of the mass was still elevated and showed no visible scars from the diathermy applications. Three years after operation it was noted that obliteration of some retinal vessels had progressed from the periphery toward the disc. Two inferior arterioles were completely occluded, and all other arterioles were rather narrow. These vascular changes appeared to result from the slow progression of preexisting vascular damage and not as a consequence of the diathermy applications. Central vision was still the same, but the visual field was somewhat constricted.

Comment

This section includes the discussion of some remarkable features of our case and a brief review of pertinent data from the literature. In our case, three points deserve further attention: the bilaterality of the condition, the ophthalmoscopic and retinoscopic diagnosis of a choroidal elevation in the macular area, and the treatment of choroidal hemangioma.

The bilaterality of a retinal detachment does not rule out an idiopathic origin. It is the fact that a retinal break cannot be found in either eye at any time which is strongly suggestive of some type of secondary (nonidiopathic) retinal detachment. As a rule, this condition has several other characteristics in addition to the absence of retinal breaks. First, this type of retinal detachment is often smooth, and, consequently, the choroidal pattern is more clearly visible than is usual through a detached retina. This was the case with our patient, and it explains why several ophthalmologists repeatedly examined her eyes and failed to recognize the bilateral retinal detachment. In the left eye it was diagnosed fairly early, perhaps because vision in the other eye had already decreased to 20/200. It is almost certain, however, that when a retinal detachment was finally detected in the right eye it had been present for many months. Vision in the right eye had deteriorated from 20/30 to 20/200 eighteen months previously, and we found a demarcation line at the upper limit of the detachment, which indicates a retinal detachment of long standing and slow progression.

Another characteristic of secondary (nonidiopathic) retinal detachment is that, as a rule, the subretinal fluid shifts rapidly with changes of position of the patient's eyes or head. With idiopathic detachments the shift also occurs, but often more slowly

and to a smaller degree. This explains why on three occasions attempts to release subretinal fluid from the eyes of our patient were unsuccessful.

As far as could be determined, our case is the only one in the literature showing bilateral isolated choroidal hemangiomas. There are several case descriptions, however, where the presence of a bilateral choroidal hemangioma may be retrospectively suspected. Three patients have been observed with bilateral nevus flammeus and bilateral buphthalmos [3,10,18] two of these [3,10] also showed bilateral telangiectasias of the conjunctiva. Two were not examined histologically,[3,18] but in the third instance [10] a choroidal hemangioma was found in one eye. A choroidal hemangioma may well have been present in all the buphthalmic eyes of patients with nevus flammeus. Another report [14] mentions a 17-year-old girl with nevus flammeus and a whitish tumor in the right eye, which was blind. A choroidal hemangioma was found in it after enucleation. As bilateral juvenile glaucoma was present, it is possible that it was the result of a bilateral choroidal hemangioma. Another description [28] refers to a patient who showed typical signs of tuberous sclerosis. One eye was excised because a tumor was seen in the fundus. Histological examination uncovered a choroidal and a retinal hemangioma and lesions typical of tuberous sclerosis. Retinal angiomatosis and a choroidal tumor were diagnosed in the other eye with the ophthalmoscope. The choroidal tumor was located in the lower temporal quadrant and was presumed to be a choroidal hemangioma. Without question, too little attention has been paid to careful examination of the fellow eye in cases suspected of choroidal hemangioma, as many case descriptions do not even mention the other eye.

The second interesting feature of our case is related to the ophthalmoscopic and retinoscopic diagnosis of a choroidal elevation in the macular area. In spite of multiple fundus examinations by a number of different ophthalmologists, the mass in the left eye was observed for the first time six months after the refractive error indicated that the tumor had reached a thickness of nearly 4 mm. (11 D.). The diagnosis in the right eye was made seven months after the tumor had reached the same thickness. Even then, the presence of these tumors was asserted by some ophthalmologists and denied by others, indicating that a large choroidal hemangioma may be extremely difficult to diagnose with the usual methods of observation, in spite of its obvious location. An ophthalmoscope with a strong light and stereopsis is particularly useful for detecting a choroidal tumor which is located under a detached retina without adhering to it. In both eyes of our patient, this peculiarity had completely hidden the tumor to all observers equipped with either a monocular ophthalmoscope or an instrument lacking powerful illumination.

Even if no tumor is seen with the ophthalmoscope, a gradually increasing and otherwise unexplained hypermetropia is suggestive of a choroidal hemangioma of the posterior pole [19]; this is illustrated by our own case. The graphs of Figure 2 indicate that increasing hyperopia started in the left eye between 1932 and 1941, and the rate of growth increased during the following years. A similar curve made for the right eye suggests that the tumor probably started growing before 1932 and increased at a slower rate than on the left side. When we examined both eyes in 1954, the tumor in the right eye was considerably smaller than that in the left, in spite of the fact that the larger mass started to grow several years after the smaller one. Vision in the right eye decreased markedly in 1952, probably as a result of retinal detachment. This was about five years after the hyperopia had increased above 9 D. (Fig. 2). In the left eye the visual loss resulting from retinal detachment occurred a few months after

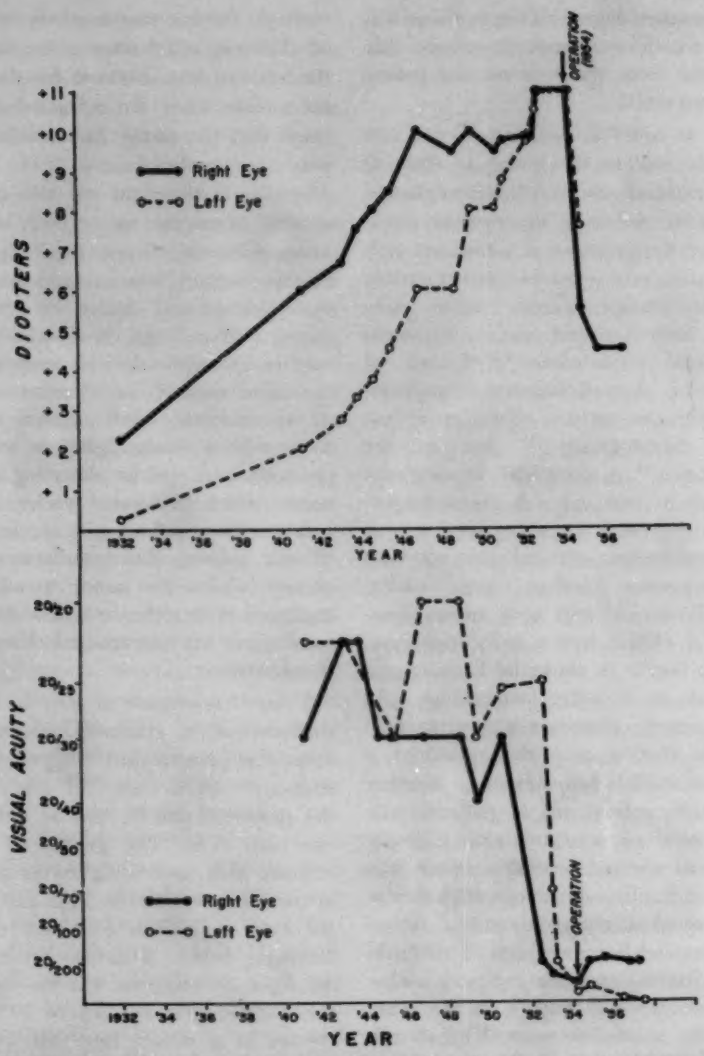

Fig. 2.—The upper diagram represents the changes in refractive error for each eye from 1932 to 1957. It took 20 years for the right eye to progress from +2.25 D. to +11.00 D., whereas it took only 9 years for the left eye to undergo a similar change. In both eyes there was a sharp decrease of the hyperopic refractive error after surgery. This change was more marked after diathermy (right eye) than after biopsy (left eye).

The lower diagram represents the variations in corrected visual acuity over a 17-year period. For a number of years the patient had noted that the right eye was poorer than the left. In fact, since 1946, vision in the right eye could not be improved above 20/30, and this corresponds to the time when the tumor in the right eye became over 3 mm. thick in the macular area. The sudden loss in visual acuity to the 20/200 level occurred in both eyes as a result of retinal detachment. Slight visual improvement was noted after operation. In the left eye, however, the retina redetached later and there was loss of light perception.

the right eye was similarly affected, and this was about three and a half years after the hyperopia had increased above 8 D. From these observations we conclude that a slowly growing hemangioma of the choroid, located at the posterior pole, may

cause a gradual increase of hyperopia with good vision preserved for a long time. According to Kreibig,[19] even an amblyopic eye which is more hypermetropic than the fellow eye may contain a choroidal hemangioma which cannot easily be detected with the ophthalmoscope.

The effects of the surgery, which was performed on both eyes in 1954, are also indicated in the graphs (Fig. 2). After diathermic treatment, vision in the right eye improved slightly and the hyperopia decreased from 11 to 4.50 D. After biopsy of the left eye, vision improved a little and then diminished gradually, until three years postoperatively there was no perception of light; the hyperopia had diminished from 11 D. to 7.50 D.

The third point of interest in our case relates to the treatment of choroidal hemangioma. The only "therapy" widely recommended in the literature is enucleation. However, Hallerman[15] has tried surface and perforating diathermy, with poor functional results, and Paton[35] has used galvanopuncture of the tumor, also with discouraging effects. Dufour[9] feels that diathermic destruction of a choroidal hemangioma might be advisable in selected cases, but Kreibig[19] mentions that this treatment is of no avail. Carreras Matas[7] succeeded in removing surgically a choroidal hemangioma through a scleral incision, thinking it was a Cysticercus. X-rays, radon seeds, or radium are untried in the therapy of this condition but might be successful in early cases. However, the disadvantages of radiation have to be considered. It is our feeling that careful diathermy is probably the therapy of choice, although more experience is needed to evaluate it better. It may be that in advanced cases no therapy will prove of value and that diathermy can give hope for a permanent cure only in early cases. Destruction of the tumor by this method demands accurate localization in order to avoid applying diathermy to uninvolved parts of the choroid. This is best accomplished with the help of indirect ophthalmoscopy. Needle electrodes of proper length are used under constant ophthalmoscopic control, according to a technique which will be discussed in further detail in a forthcoming publication.

A review of the literature indicates that hemangioma of the choroid is a relatively rare disease. Leber[23] published the first histologically controlled case in 1868. In 1952 Danis[8] found only 61 cases with histological diagnosis. About half had associated hemangiomas elsewhere,[8,24] most commonly skin nevi of the face in the area innervated by the first or second branch of the trigeminal nerve. Several cases also showed neurological signs, the choroidal hemangioma being then part of a Sturge-Weber syndrome.[1,2,8,10] It is probable that choroidal hemangioma is more frequent than has been hitherto suspected, as five cases were uncovered by routine histological examination in a series of 4500 enucleated eyes.[16] If all eyes removed for glaucoma or expulsive hemorrhage were systematically examined, there is no doubt that more cases would be found.[8,12,24,39] However, some of the cases published as isolated hemangioma of the choroid may have been associated with other undetected lesions, because in many instances there is no mention of a systemic examination.

The size of choroidal hemangiomas varies from 2 to 17 mm. in diameter and from 1 to 9 mm. in thickness.[39] Histologically the tumor shows numerous sinuses lined with endothelium, forming a capillary rather than a cavernous hemangioma.[36,47] There often is a proliferation and degeneration of the retinal pigment epithelium. A layer of fibrous tissue is nearly always present between the tumor and the retina,[8,13,29,39,44] and ossification of this layer has been observed in 50% of the cases.[11,20,30] The tumor is seldom adherent to the retina and never extends into it, being nearly always separated from it by serous fluid. The retina overlying the tumor frequently shows cystic degeneration with vacuolation

and some gliosis. It has been stated that most choroidal hemangiomas are simple hemangiomas.[27] If this is so, their origin and development may be explained on the same basis as skin hemangiomas, which tend to follow the distribution of nerves.[48] The growth of blood vessels is believed to be regulated by the vasomotor nerves. In the area of the meninges, eyes, and face, these nerves generally follow the distribution of the fifth cranial nerve. Impairment of vasomotor nerves during the development of blood vessels may cause them to dilate, bringing about an increased tension in the capillaries. This process stimulates proliferation of the capillaries, producing a hemangioma.[27] The predilection for the area innervated by the first and second branches of the fifth cranial nerve is unexplained. In the choroid, hemangiomas nearly always begin at the macula, as can be seen from examining specimens of early cases.[27] The reason for this may be related to the particularly dense network which the choriocapillaris normally forms in the macular area. What causes the tumor suddenly to start growing is unknown, as it is for most tumors elsewhere in the body. It is possible that, in fact, the growth is not sudden but rather gradual and continuous, as indicated by the history of our case. Clinical symptoms appear suddenly when vision is severely impaired, generally by the occurrence of either retinal detachment or glaucoma. It seems certain that a number of such tumors stop growing at an early stage and remain quiescent for years, and possibly throughout life, as they are sometimes discovered by accident in routine pathological examination of an eye. However, most of the cases reported seem to have increased in size with advancing years.

Enucleation was performed for a variety of reasons in the cases reported, most often because the presence of a malignant intraocular tumor was suspected. The majority showed glaucoma, and some authors believe that monocular buphthalmos is often associated either with choroidal or retinal hemangiomas [1,2,12] or with von Recklinghausen's disease.[12] However, in one instance of buphthalmos associated with nevus flammeus no choroidal hemangioma was found in the pathological specimen.[40] The explanation may lie in the fact that a flat choroidal hemangioma sometimes becomes invisible after fixation.[39] Several authors report that the eye had to be enucleated because of expulsive hemorrhage following an intraocular operation.[1,2,10,28] An accidental contusion of a globe containing a choroidal hemangioma is known to have precipitated glaucoma with intraocular hemorrhage.[51]

A diagnosis of presumption is relatively easy when a nevus flammeus is present but is much more difficult when the choroidal hemangioma is isolated. Most authors claim that prior to enucleation it is impossible to make such a diagnosis. Previous reports indicate that the clinical characteristics of choroidal hemangioma are as follows. There seems to be no sex preference and no predominance of right or left eye selection. The tumor starts at an early age and grows slowly; it seems more rapidly progressive in cases associated with a nevus flammeus, when enucleation is generally done before 25 years of age, than in isolated choroidal hemangioma, when excision of the globe is often performed around 50 years of age.[39] In 24 of 26 cases the tumor was located at the posterior pole, generally affecting the macula [33]; it is nearly always lens- or dome-shaped. As it rarely mushrooms through Bruch's membrane,[12] it does not tend to adhere to the retina. The color of the hemangioma varies, probably because a sheet of fibrous tissue tends to grow over its surface, between the detached retina and the tumor. Colors described vary from white to pale gray and from yellow to red; it is often salmon pink. Pigmentation is rarely seen on the surface of a choroidal hemangioma or around it. The retina overlying the tumor frequently shows cystic degenera-

tion [12,17,33,37,38,52] as well as detachment without adhesion to the growth. Dilated vessels may appear on the tumor; adjacent choroidal vessels may be similarly dilated,[17,41] and also any nearby vortex ampulla.[41,49] Ossification of the fibrous plate covering the tumor has been detected by x-ray examination as a ring of regular shape.[21] Even in the absence of nevus flammeus, telangiectasias may be visible by external examination of the eye and adnexae.[3,10,19,39] Glaucoma generally occurs at a late stage in choroidal hemangiomas, as it does in malignant tumors of the choroid. In juvenile unilateral glaucoma, particularly if associated with buphthalmos,[8] the presence of a choroidal hemangioma must be considered. As there may be associated lesions in the pia mater, a careful neurological examination is necessary in all cases. Skull x-rays may show intracranial calcifications indicative of hemangioma in that location,[39] even when no nevus flammeus is present. It should be noted that transillumination of the eye is an unreliable diagnostic test, as it may be positive or negative with either a benign or a malignant choroidal tumor. Finally, transient spontaneous improvement of vision has been noted with choroidal hemangioma [41,49] and may have some diagnostic value.

Several patients with choroidal hemangioma were examined ophthalmoscopically before excision of the globe. Some showed a fairly early stage of the tumor development,[6,7,9,11,15-17,19,24,32,37-39,41,49,52] and others exhibited late stages, often with extensive retinal detachment and advanced glaucoma.[1,4,5,8,10,12,14,22,26,29-31,34,35,43,45,46,50] It seems that, in the absence of a nevus flammeus, a clinical diagnosis later verified by histological examination is recorded only once in the literature.[15] This patient, however, had an extensive homolateral nevus on the shoulder blade. Some authors [19,25,41,52] state that, before the occurrence of symptoms which necessitated enucleation, the fundus appeared normal. It is probable that an inconspicuous lens-shaped choroidal hemangioma was present but escaped observation. The usefulness of stereoscopic indirect ophthalmoscopy with a strong light should be once more emphasized in this connection.

Biopsy, while not to be undertaken lightly, should be part of our diagnostic armamentarium; it was reported in one other case.[7] There is probably a significant danger, if the tumor should be a melanoma, of disseminating tumor cells into the orbit at the time of surgery or of leaving a pathway through the sclera for their subsequent extraocular extension. However, if considerable doubt exists regarding the diagnosis, and especially if the patient refuses enucleation, biopsy must be considered.

The differential diagnosis should include choroidal malignant melanoma, choroiditis, and disciform degeneration of the macula. Choroidal hemangioma is usually seen in a younger age group than either malignant melanoma or senile disciform degeneration of the macula. It grows slowly, whereas a malignant choroidal tumor in a young patient often tends to grow quickly. A malignant melanoma may be further distinguished by its slate or brown color, its abnormal pigmentation, and, frequently, by its localized adhesion to the detached retina. Vitreous haze and abnormal pigmentation of the choroid and retina often accompany an inflammatory lesion but are absent with choroidal hemangioma. Intraocular ossification is to be expected only with inflammatory lesions and with choroidal hemangioma,[21] although Fehr [11] reports an exceptional case where it was observed in an eye containing a slow-growing malignant choroidal melanoma with marked necrosis. The differentiation between choroidal hemangioma and juvenile disciform degeneration of the macula may prove difficult, but the degenerative disease tends to cause more subretinal hemorrhage and more pigmentary disturbance in the choroid and retina. A salmon-pink nonpigmented dome-shaped mass in

the macula of a young patient should always be suspected of being a choroidal hemangioma, particularly when central vision is retained for a long period of time.

Summary

A case history is presented of a patient with bilateral hemangioma of the choroid without signs of hemangioma elsewhere. Progressive bilateral hyperopia from +2.25 D. sphere to +11.00 D. sphere in the right eye and from +0.25 D. sphere to +11.00 D. sphere in the left eye was followed in retrospect by tracing the prescriptions for glasses given by many different examiners during a 25-year period.

A biopsy of the choroidal tumor in the poorer eye was performed, and microscopic examination established the diagnosis of choroidal hemangioma. The feasibility and usefulness of this type of biopsy in a selected case is thereby demonstrated. Diathermy coagulation of the hemangioma in the other eye was successfully performed, with maintenance of useful vision and disappearance of the retinal detachment. This favorable result, with follow-up period of more than three years, indicates the value of diathermy, at least in the early stages of the disease. The ophthalmoscopic diagnosis of an isolated choroidal hemangioma is difficult but can be helped by use of a stereoscopic indirect ophthalmoscope with a strong light. The tumor is generally lens- or dome-shaped and is located at the posterior pole. It has a pale color, either pink or gray, with little or no abnormal pigmentation. Dilated vessels may be seen on the tumor and in the surrounding choroid. The overlying retina is frequently cystic, detached, and not adherent to the choroidal tumor. Intraocular ossification is frequent and may be detectable by x-rays. When there are no indications of systemic involvement, the following additional signs are valuable if present: conjunctival telangiectasias, glaucoma, early age of onset, and slow progression. Any salmon-pink smooth mass in the macular area of a young patient, with slowly progressive hyperopia and good vision retained for years, must be suspected of being a hemangioma.

Pictures in this article were drawn by William Stenstrom.

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The Scleral Buckling Procedures

II. Technical Difficulties of Primary Operations

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In the first article of this series we defined what is meant by scleral buckling; this was followed by a description of four basic types of scleral buckling and a brief outline of the pre- and postoperative care of a standard case. Many cases, of course, are not standard, and the handling of these atypical cases often creates technical difficulties. In this article, the management of such difficulties is discussed. The first part deals with problems which may occur during the performance of the scleral buckling, and the second, with problems sometimes encountered at the end of the procedure. Reoperations will be considered in subsequent articles.

Problems Occurring During a Scleral Buckling Operation

During operation, difficulties may arise as a result of thinness of the sclera, poor exposure, and interference with the vortex veins or the long ciliary arteries and nerves.

Thinness of the sclera is not infrequent and is often accompanied by equatorial staphyloma. It is unnecessary and often impossible to remove a layer of sclera in a staphylomatous area. Light diathermy is applied without scleral excision, and the operation is continued as usual.

If a mattress suture is passed in thin sclera, it tends to cut through the scleral fibers when a knot is tied. This can be prevented to a certain degree by placing a small plate, cut from a polyethylene tube, under the suture so as to protect the weak portion of the sclera (Fig. 1, *A* and *B*).

Sometimes the sclera is thin in the immediate vicinity of the buckle but not further away; it is then advisable to place the suture further away than usual from the scleral incisions (Fig. 1, *C*). If the sclera is thin everywhere, it is essential to take special precautions. The thinness of the sclera may vary from place to place; this is indicated by changes in its bluish coloration. A careful excision of sclera should be done only in the whiter zones in order to obtain an even thickness of sclera over the area to be treated. The diathermy should be light and applied with great care so as to avoid perforation of the globe. As the placement of scleral sutures in very thin sclera is difficult, a strict minimum of such sutures should be used. Bites of normal length may not hold; it is therefore advisable to take long bites in the sclera (Fig. 1, *D*). If this places the knot at less than 10 mm. from the limbus, or in any other circumstance where the knot is so located, the suture should be placed in such a way that the knot is tied posteriorly. This will prevent its eroding through the conjunctiva postoperatively and being a potential cause of irritation and late infection.

Long bites in thin sclera do not receive adequate protection from a polyethylene plate as described above. It has been found more useful, in such cases, to use a similar plate parallel to the scleral incisions (Fig. 1, *D*). When the sclera is thin everywhere, a circling polyethylene tube must be used, as this is the only safe method for obtain-

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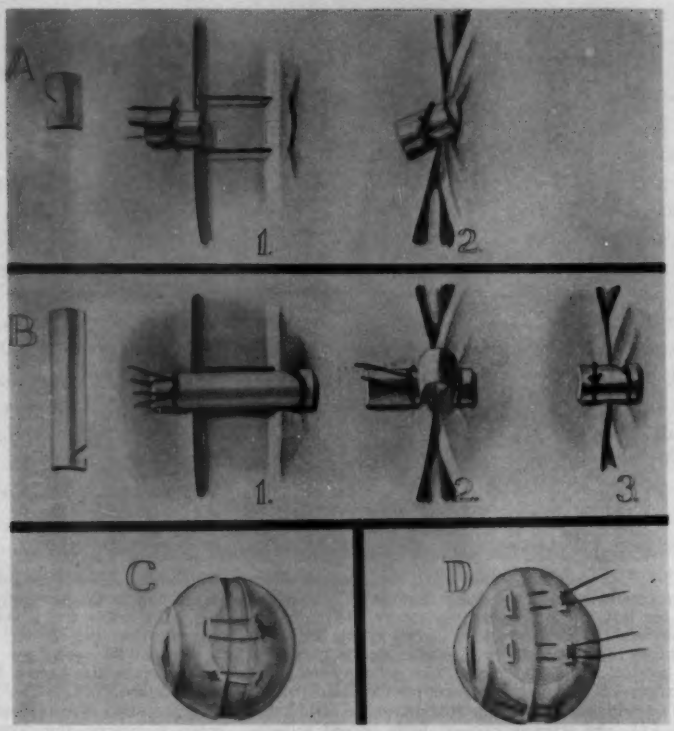

Fig. 1.—Placement of mattress sutures in weak sclera. *A*, when the sclera is weak on one side of the lamellar resection, a small polyethylene plate is used for preventing the mattress suture from cutting through the sclera. This plate is made with a portion of tube cut lengthwise and notched on the side, as illustrated on the left. (*1*) The plate is placed under one of the loops of the suture. (*2*) The plate is shown in position when the suture is pulled up over the tube and the knot is tied. *B*, when the sclera is weak on both sides of the resection, a longer polyethylene plate is used, as illustrated on the left. (*1*) The plate is under the suture loops. (*2*) The plate bends when the suture is pulled up; it is straightened by pulling on the free end of the plate with forceps. (*3*) The plate is in place and suitably shortened; the knot has been tied. In practice it has been found that the long polyethylene plate (Fig. *B*) gives a more secure protection than the short plate (Fig. *A*). *C*, the resection passes through thin sclera (dotted area). In the two mattress sutures represented, the scleral bites are placed away from the edge of the resection, in sclera of normal thickness. In the upper suture, the anterior bites are less than 10 mm. from the limbus, and, therefore, the knot is placed posteriorly. *D*, the resection passes through an extensive area of thin sclera (dotted) which causes the spherical shape of the globe to be distorted. Sclera is resected only as needed in the thin area. The suture bites are much longer than usual, and the sutures are passed through small polyethylene plates; this prevents the sutures from cutting through the thin sclera. The knots are placed posteriorly because the anterior bites are closer than 10 mm. from the limbus.

ing an adequate buckling effect with very few scleral sutures.

Excessive thinness of the sclera may be artificially created, either by excessively deep scleral incisions when the scleral resection is started or by excision of too thick a layer of this tissue. In all such cases, the possible damage resulting from hernia and rupture of the choroid must be kept in mind. In order to avert such grave complications, it is essential to eliminate any undue pressure on the globe. If the intraocular pressure is elevated, it may be well to lower it; this is accomplished either by releasing some of the subretinal fluid through a very small opening or by a carefully performed paracentesis. In addition, a mattress suture is placed in the lips of the scleral incision over the bulging area and a small sheet of polyethylene 0.0015 in.

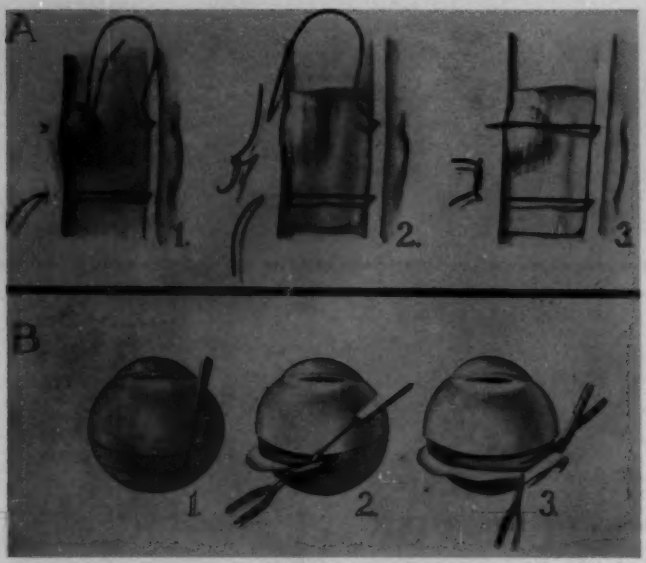

Fig. 2.—*A*, protection against weak areas in the sclera. (*1*) One of the incisions demarcating the resection is made too deep, causing a choroidal hernia as soon as the surgeon attempts to place the last bite of a mattress suture. (*2*) The needle is withdrawn, and a small sheet of polyethylene 0.0015 in. thick is placed in the bed of the resection over the choroidal hernia. The suture is then passed in a direction almost parallel to the edge of the resection. (*3*) The mattress suture is pulled up over the polyethylene sheet; this prevents the hernia from becoming larger. *B*, method for resecting the sclera when exposure is poor. (*1*) The posterior incision is made with a cutting spatula. (*2*) The dissection of the strip is continued with a scarifier. (*3*) The strip is excised with curved scissors. When necessary, the posterior incision may be omitted (*1*); Steps *2* and *3* are then carried out as described.

thick is introduced under the suture (Fig. 2, *A*).

Bulging of choroid through an excessively deep scleral incision, used to outline the lamellar resection, tends to occur when the mattress suture is being passed through the sclera. Therefore, when a scleral incision has been made too deep, the bite of the mattress suture is placed parallel to the scleral incision instead of perpendicular to it (Fig. 2, *A*). Whenever there is a risk of rupturing the globe, it is safer to grasp the sclera with toothed forceps while passing the needle and suture through it. This practice is advisable in spite of the fact that toothed forceps damage the sclera and should, as a rule, be used only to grasp the scleral lamella.

A second difficulty sometimes encountered is that of exposing the portion of the sclera which corresponds to the retinal breaks; such may be the case when the orbit is smaller than usual in relation to the size of the globe or when the breaks are posteriorly located. Poor exposure is oftener met with on the nasal side. The situation is often worse when three or four extraocular muscles are detached, because the globe then becomes proptosed and, in that position, it is harder to expose its posterior aspect by rotation. When the eye is gently pressed back into its socket, the posterior part of the sclera is more easily exposed than when the globe is proptosed. The surgeon may be forced by the difficulty of exposure to modify the buckling technique to some extent. For instance, it may be nearly impossible to use a Desmarres scarifier for making the scleral incisions which outline the scleral lamella. These incisions are then made with a cutting spatula, and dissection of the lamella is completed with a scarifier (Fig. 2, *B*). If the posterior incision can-

not be made safely with a cutting spatula, the anterior incision and the dissection of the scleral lamella are performed as described and then the lamella is severed from the sclera with curved scissors. The placement of mattress sutures in a posteriorly located area demands the use of a small sharp needle, for example, the Grieshaber No. 82/5, and of a fine curved needle holder, such as the model made for this purpose by Grieshaber.[1] If great difficulty is experienced, it may be advisable to use a single rather than a mattress suture. As additional sutures are easier to place after the release of subretinal fluid, a minimum number of sutures should be used before its release.

A third problem is interference with the vortex veins, long ciliary nerves, and long posterior ciliary arteries. It is essential to avoid cutting, pricking, or tearing them. The long ciliary vessels and nerves run in the sclera under the lateral and medial rectus and can often be seen. It is easy, therefore, to avoid cutting them when dissecting off the scleral lamella, and no diathermy should be applied directly over them.

The vortex veins are generally four in number and are said to emerge from the sclera at points located roughly 19 mm. from the limbus on either side of the superior and inferior rectus muscles. The vortex veins are notably inconstant both in number and in location. It is not unusual, therefore, for an eye to show more than four vortex veins, and their point of emergence from the sclera may vary between 14 and 22 mm. from the limbus. One fairly constant feature, however, is that the point of emergence of the upper temporal vein is hidden under the temporal portion of the superior oblique tendon. When the resected strip of sclera has to run through the point of emergence of a vortex vein, three cases may be considered.

In the first case, the vortex vein is located in the posterior part of the area to be resected (Fig. 3). One dissects around the vein, being careful to avoid damaging any of its several intrascleral branches; for this reason, it is necessary to make the resection more superficial in this area. In the second case, the point of emergence of a vortex vein is in the middle of the strip to be resected. It is often possible to change slightly the course of the resection in order to have it run either more anteriorly or more posteriorly. If, however, this is impossible, the vortex vein has to be sacrificed. It is first obliterated with diathermy, then tied a few millimeters from its point of emergence and severed. If it is cut too close to the sclera, it may retract into the globe and cause a massive intraocular hemorrhage. Experience has shown that severing one or even two vortex veins is generally without consequence, but, of course, vortex veins should be cut only when absolutely necessary. This is particularly true in reoperations, because the number of veins left patent as a result of

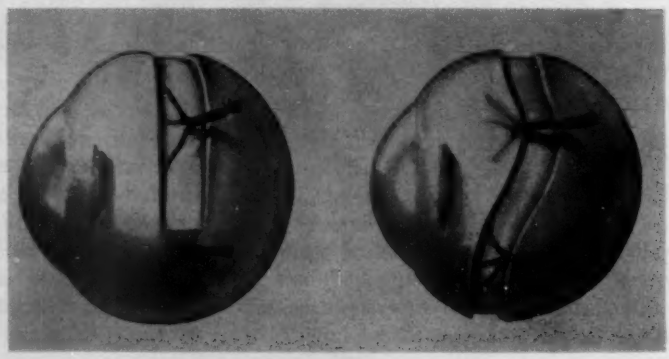

Fig. 3. — Handling of vortex veins. On the left, the resection has to pass through a vortex vein which is cut and tied. Care must be taken not to traumatize the branches of the vein when applying diathermy to the bed of the resection. On the right, the course of the resection is slightly modified in order to pass either in front of a vortex vein (below) or behind it (above).

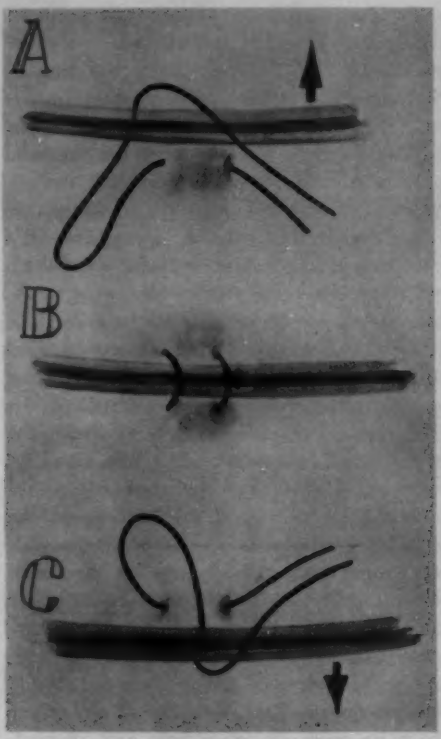

Fig. 4.—Anchoring of a circling tube which is not buried in a scleral resection. *A*, if the circling tube is located anterior to the equator, it tends to slide anteriorly (arrow) and must be anchored to the sclera by an equatorial suture. *B*, if the circling tube is at the equator, it may slide either way and must be immobilized under a mattress suture. *C*, if the circling tube is behind the equator, it tends to slide posteriorly (arrow) and must be anchored by an equatorial suture.

previous surgery is unknown. In the third case, the resection is posterior to the point of emergence of the vortex vein and can be carried out under the vein by gently retracting it to the side. When diathermy is applied to the resected area of the sclera under the vein, care should be taken not to damage it or its recurrent branches, which run posteriorly in the sclera across the resected area.

Whenever the lamellar scleral resection is in the vicinity of the point of emergence of a vortex vein, its intrascleral branches will be found to run across the resected area. No diathermy should be applied over these branches; they are easy to avoid, as the scleral resection makes them readily visible. Failure to observe this precaution may cause late intraocular hemorrhage. Another important point relative to vortex veins is that in the course of the surgical procedure one of them may collapse temporarily, probably as a result of the following mechanism: Raised intraocular pressure may collapse the vortex ampulla and, at the same time, pressure with a retractor or other instrument on the orbital tissues may prevent the vein from filling through back-flow. In this case, it is difficult or impossible to see the vein, and it may unwittingly be destroyed. Care should also be taken not to exert unnecessary pressure or traction with the retractor on the orbital tissues, as a vortex vein may be crushed or torn in this fashion.

Finally, it should be remembered that whenever a circling tube is buried over less than half the circumference of the globe it may slide either forward or backward, thereby diminishing the height of the buckle. When the tube slides forward, it is retained by the insertion of the rectus muscles. When it slides backward, there is no structure to retain it except the optic nerve. In moving back, the tube may occlude one or more vortex veins beyond their point of emergence from the sclera. Whenever a circling tube has a tendency to slide, its exposed portion should be anchored to the sclera in each quadrant (Fig. 4).

Problems Occurring at the End of a Scleral Buckling Operation

When the mattress sutures are drawn up and locked, and before the second knot is placed on any of the sutures, it is essential to check the appearance of the fundus carefully with the ophthalmoscope.[1] As incomplete release of the subretinal fluid has been discussed in our first publication, there remains only one other problem to consider, namely, that of a buckle which inadequately covers the retinal breaks.

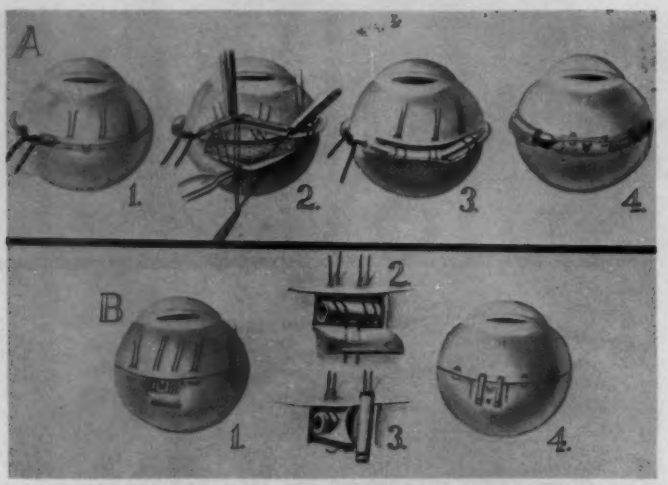

Fig. 5.—Methods for treating a break which is incompletely covered by the buckle. *A*, undermining procedure. (*1*) The circling tube is in place. Ophthalmoscopy shows that a break (represented on the sclera) is on the posterior slope of the buckle. (*2*) The circling suture and three mattress sutures are loosened; the posterior edge of the scleral resection is undermined, and additional diathermy is applied to the undermined area. (*3*) The knot on the circling suture is untied; a polyethylene sleeve (PE-205) of appropriate length is passed over the circling tube and placed in the undermined area. (*4*) If ophthalmoscopy indicates that the break is better covered by the widened buckle, the mattress sutures and circling suture are tied. *B*, trap-door procedure. (*1*) The circling tube is in place, but ophthalmoscopy indicates that a break is located more posteriorly than the buckle. A trap door is made in the sclera over the location of the break; diathermy is applied in the thinned area, and two mattress sutures are placed as indicated. (*2*) A short polyethylene tube of appropriate length and diameter is placed under the sutures and anchored to the base of the trap door by an additional mattress suture. (*3*) The mattress suture which anchors the short tube is tied and cut, and the two other mattress sutures are tied over polyethylene plates. (*4*) Appearance of the globe after completion of the procedure.

It is most disturbing to note that at the end of the operation a break is partly or completely located posterior to the buckle itself. If the break is on the posterior slope of the buckle, it may be completely hidden from view by the ridge of the scleral buckling. Whenever the buckle hides a break either partly or completely from view, the buckle should be moved toward the disc. This may be accomplished either by undermining or with a trap door in the sclera.

The undermining is used when a slight correction in the position of a circling tube is all that is required (Fig. 5, *A*). The mattress sutures located in the area concerned are loosened. With use of a Desmarres scarifier, the posterior edge of the scleral resection is undermined over a length of no less than 15 mm. and a width which varies according to the need without exceeding 3 to 4 mm. The thickness of sclera left in place in the undermined area is the same as in the area of the lamellar scleral resection; it is similarly treated with diathermy. As a rule, the mattress sutures are not disturbed by the undermining and do not have to be replaced. The circling suture, and as many mattress sutures as necessary, are loosened so that a length of polyethylene tube 5 mm. to 8 mm. long and of large diameter (PE-205) can be passed, like a sleeve, over the circling tube and placed in the undermined area over the location of the break to be more adequately covered. The mattress sutures and the circling suture are drawn up again and locked; this creates a higher and wider buckle in the area corresponding to the polyethylene sleeve. The fundus appearance is checked and, if found satisfactory, the operation is completed as usual.

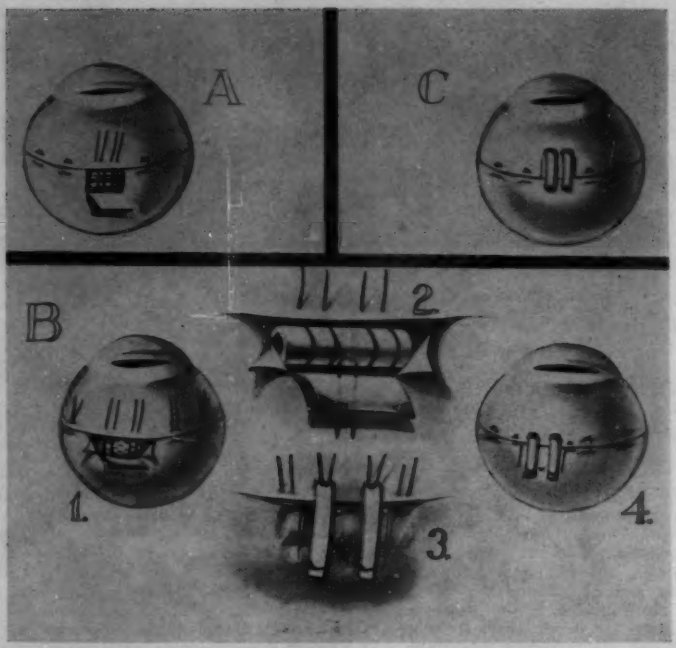

Fig. 6.—Modifications of the trap door procedure. *A*, a broad trap door may require the use of two short polyethylene tubes placed parallel to each other. *B*, after a trap-door procedure is completed, ophthalmoscopy may show that its length is insufficient. (*1*) The short polyethylene tube is removed; the edges of the trap door are dissected as indicated, and diathermy is applied in the undermined areas. (*2*) A longer tube is placed under the mattress sutures and anchored to the base of the scleral flap. (*3*) The suture anchoring the tube to the flap is tied; then the other two mattress sutures are tied over polyethylene plates. The undermined edges are held in place by additional mattress sutures. (*4*) Appearance of the globe after completion of the procedure. *C*, when a trap door has to be made anterior to the circling tube, the knots on the mattress sutures are placed posteriorly.

If the correction is insufficient, the sutures must be loosened again, the undermining extended somewhat further back, and an additional row of diathermy applied. If this is still insufficient, the undermining should be transformed into a trap-door operation.

The scleral buckling with a trap door in the sclera has been described previously.[1] This procedure is a useful adjunct to close a retinal break which is not on the buckle. As a rule, it is made by using one of the existing free edges of the lamellar resection as the edge of the trap door (Fig. 5, *B*). Its width and length depend on the size and location of the retinal break; when it has to be placed over an existing mattress suture, the latter must be removed. Diathermy is applied to the thinned sclera under the trap door, and mattress sutures are placed from one edge of the scleral resection to the base of the trap door. A polyethylene tube of appropriate diameter and length is introduced under the sutures. It is important to secure the tube by a mattress suture which is tied through the base of the scleral flap, as indicated in Figure 5, *B*, (2), (3), and (4). This additional suture prevents the short tube from rolling forward in the groove formed by the circling tube. If subretinal fluid is present, it should be released by methods previously described.[1] When there is little or no fluid, the circling suture should be loosened in order to permit easy closure of the mattress sutures on the trap door, which are generally tied over polyethylene plates. It is essential to check the ophthalmoscopic appearance before tying the

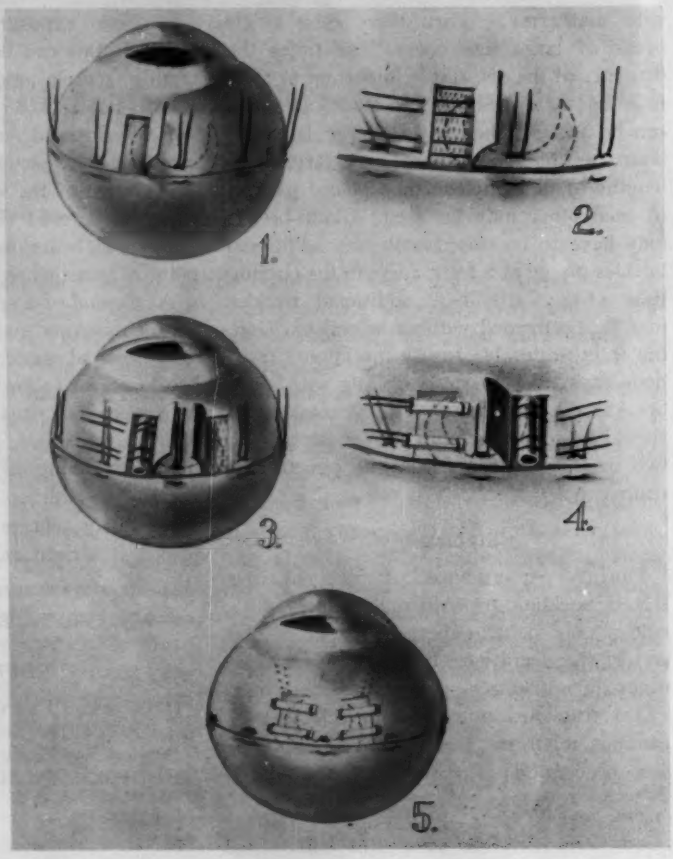

Fig. 7.—Method for closing a giant break. (*1*) After the circling tube is in place, the lateral limits of the giant break are determined by ophthalmoscopy. A trap door is then made in the sclera to close off one side of the giant break. (*2*) The area which is under the trap door is covered with diathermy, and additional mattress sutures are placed as indicated. (*3*) A polyethylene tube of appropriate length and diameter is placed under the mattress sutures. A similar trap door is made to cover the other side of the giant break. (*4*) The mattress sutures on the trap door at the left are pulled up over polyethylene plates; mattress sutures are placed on the trap door at the right, and a polyethylene tube is inserted under the sutures. (*5*) The two trap doors are closed; their anterior sides are connected to the ora serrata by a double row of surface diathermy applied with a blunt point and extending to 5 mm. from the limbus.

second knot on the mattress sutures, and if the buckle created by the trap-door procedure is not extensive enough this should be corrected. If the flap is too narrow, it should be widened and additional diathermy added on the thinned sclera; in many such cases, the mattress sutures on the scleral flap must be removed and new sutures placed more posteriorly. A polyethylene tube of larger diameter is introduced under the widened flap; if necessary, two lengths of tube can be used side by side (Fig. 6, *A*). When the flap is too short, its edges are undermined and treated with diathermy (Fig. 6, *B*). A longer, polyethylene tube is placed under the scleral flap, and its undermined edges are secured with additional sutures as required.

If the buckle is so placed that one part of the break is on its anterior slope and the other part is between the buckle and the ora serrata, it may be necessary to cover the anteriorly located portion of the break more adequately. For instance, a trap door may be added anterior to the circling tube, following the technique described above. Whenever the trap door is very anteriorly located, one should be careful to place the knots of the mattress sutures posteriorly (Fig. 6, *C*).

When one or more breaks are completely anterior to the buckle, several cases are to be considered. When the breaks are multiple and small, it may be best to wall off the area with diathermy without attempting to close all the breaks.[1] If there is only one break of small size, one may decide either to close it with a separate trap door or to wall it off

with diathermy. When there is a single break of large size (over four times the diameter of the disc), it is important to close it as tightly as possible. In some cases this can be accomplished with the regular trap-door technique. When necessary, two lengths of polyethylene tube placed parallel to each other may be used. Giant breaks may have to be closed with two additional buckles placed at a right angle to the circling tube (Fig. 7). These additional buckles may be performed without scleral excision, but it is preferable to use meridional trap-door flaps. When one is dealing with giant breaks, the anterior end of each buckle should be connected with the ora serrata by two or three rows of partially penetrating diathermy.

Summary

During performance of one of the scleral buckling procedures, technical difficulties may occur either during or at the end of the operation. Problems which may occur during surgery include the following: (1) Excessive thinness of the sclera; precautions relate to placement of the sutures and prevention of rupture of the globe. (2) Poor exposure of the area to be buckled; this can be aided by the use of a cutting spatula and a special needle and needle holder. (3) Interference with the vortex veins and the long ciliary nerves and arteries; this is to be carefully avoided. The course of the scleral buckling can generally be altered either anteriorly or posteriorly in order to avoid pressure on the point of emergence of a vortex vein.

At the end of a scleral buckling procedure ophthalmoscopy may reveal that the buckle does not adequately close all the retinal breaks. The following techniques are used to correct this situation: undermining, trap door in the sclera, and diathermy which is used for walling off some anteriorly located breaks. In addition to a circling tube, giant breaks may require two additional buckles placed at a right angle to the circling tube.

The drawings were made by William Stenstrom.

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The Sources of Fibroblasts in Corneal Wound Repair

A Quantitative Analysis

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The present study has been undertaken to determine quantitatively the extent to which transformation of corneal stromal cells and mitosis of these cells supply the healing wound with fibroblasts.* Previous investigations of the morphology of corneal wound healing have shown that most of the corneal stromal cells originally present at the wound edge were transformed into fibroblasts during the first 24 postoperative hours.[1] However, by inspection alone it appeared that there were not enough corneal stromal cells present at the wound edge to account for the increased numbers of fibroblasts to be found as wound healing progressed. Furthermore, Allgöwer [2] has stated that the early and great concentration of cells surrounding a wound cannot be attributed to cell division.

In this report evidence is presented to show that corneal-cell transformation and division provide for about 35% of the total number of fibroblasts found 60 hours after injury and that the remaining 65% may be accounted for by the transformation of monocytes to fibroblasts.

Inasmuch as the corneal stroma is avascular and relatively acellular, cells migrating into it from the limbal tissues can easily be observed. It can readily be calculated that fibroblasts cannot migrate rapidly enough from the limbal tissues to provide the source of fibroblasts found at the wound edge of central corneal wounds. With use of the fastest rates of migration for fibroblasts observed in ear window chambers in vivo, 0.29 mm. per day,[3] it can be estimated that a minimum of 10 days would be required for fibroblasts to migrate to the center of adult rat corneas, a distance of approximately 3 mm. Therefore, fibroblasts found in central corneal wounds must arise from cells already present in the cornea or from cells which migrate at a more rapid rate and then transform. The comparable estimated time for migration of monocytes from the limbus to a central corneal wound of an adult rat would be about 8 to 9 hours, 0.35 mm. per hour.[4,5]

Procedure

Adult rats weighing 250 to 400 gm. were used. The rats were anesthetized (about two minutes) with ether, and, with use of a sterile Graefe knife, a 2 mm. wound was made as near the center of the cornea as possible.

1. *Giemsa Stain.*—(*a*) Normal Animals: Counts of the cell types present at the wound edge in normally healing wounds were carried out on whole mounts of the corneal stroma. This preparation has been described previously.[1] Wounds of 0, 12, 24, 30, 36, 48, 60, 72, 84, 96, and 120 hours were analyzed. For cell counts an oil-immersion objective (total magnification, ×970) was used. The cells were counted through all depths of the corneal stroma. In this paper all cell counts are expressed as the number of cells per oil-immersion field through all depths of the corneal stroma.

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* In this paper fibroblasts are defined as long spindle- or star-shaped cells with oval nuclei which contain one or more large nucleoli (usually several).

(*b*) Colchicine-Treated Animals: For studies of mitosis the animals were injected subcutaneously with freshly prepared solutions of colchicine, with use of a dose of 2 mg. per kilogram nine hours before death.[6] This was the maximum dosage which could be given, for occasionally animals were dead or near death at the end of the nine-hour period. The eyes were prepared as previously described and were also stained with Giemsa stain.[1]

2. *Neutral Red.*—The animals were wounded in the usual manner and killed with ether at the indicated experimental periods, and the eyes were immediately enucleated. The epithelium was brushed off with a swab made of dry nonabsorbent cotton. The entire cornea, with a 1 to 2 mm. scleral flap, was cut out and rinsed in mammalian Ringer solution.† The cornea was next suspended for three hours at room temperature (20 to 25 C) in a dish containing 4 drops of 0.1% neutral red per 5 ml. of Ringer solution. This concentration of neutral red has been found to be relatively nontoxic,[8] and in these preparations the nuclei remained unstained even when the tissues were left in the neutral red solution for periods up to nine hours.

All solutions used for the living tissues were made up in water redistilled in glass. At the end of the three-hour period a strip of the cornea was so cut that the wound lay at right angles across the strip. The sections were then examined microscopically and color (Ektachrome) photomicrographs were taken (total original magnification, × 430) to record the results. The cells were then counterstained with methylene blue to stain the nucleus and the nucleoli and were rephotographed. When the sections were not counterstained with methylene blue, the results were photographically recorded in black and white (Kodak Tri-X). The sections were stained from 20 to 30 minutes in Ringer solution containing 6 drops of 0.1% methylene blue per 5 ml. of solution. It was necessary to inspect these counterstained sections at frequent intervals to avoid overstaining because the methylene blue tended eventually to stain the entire tissue blue, including the neutral red vacuoles.

Results and Comment

1. *Formalin-Alcohol-Fixed Material Stained with Giemsa Stain.*—(*a*) Normal Animals: During the first 24 postoperative hours the corneal stromal cells at the wound edge underwent marked morphological changes and became transformed into fibroblast-like cells. The gradual transition of these cells into fibroblasts is described in a previous report.[1] The region of the transformation of cells to fibroblasts was limited to a narrow border about 200μ wide on each side of the wound edge. This was equivalent to approximately one oil-immersion field (× 970).

It could be demonstrated by cell counts that it was the corneal stromal cell which gave rise to these first fibroblasts. At zero hours 49.24 cells of all types, excluding polymorphonuclear leukocytes,[9] were present per oil-immersion field through all depths of the corneal stroma.‡ Of these, about 2.5 were large monocytes.§ None of these monocytes contained nucleoli. Most of the corneal stromal cells contained no nucleoli or such very small nucleoli that it was often questionable whether they were nucleoli, specks of granular chromatin, or bits of the lacy cellular cytoplasm.

At 12 hours after injury 55.06 cells containing large nucleoli were present and were identified as follows: 7.71 (14.1%) monocytes, 0.55 (1.0%) fibroblasts, and 46.50 (84.9%) corneal stromal cells (total, 54.76) (Table 1). Cells which did not contain large nucleoli were rarely seen at any postoperative period studied.

† Composition of Ringer Solution[7]: water, 100.0 gm.; NaCl, 0.9 gm.; KCl, 0.042 gm.; $CaCl_2$, 0.024 gm.; $NaHCO_3$, 0.01 to 0.03 gm.

‡ From five to seven eyes were counted for each of the time periods studied.

§ These monocytes characteristically had large horse-shoe nuclei and dust-like cytoplasm.

TABLE 1.—*Differential Count of Cell Types with Large Nucleoli at the Wound Edge at Various Time Periods After Injury* *

Wound Period, Hr.	Cells with Large Nucleoli, No.	Fibroblasts, No.	Monocytes with Large Nucleoli, No.	Corneal Stromal Cells with Large Nucleoli, No.
0	0.0±0.00 †	0.0±0.00	0.00±0.00	0.00±0.00
12	58.06± 8.82	0.55± 0.55	7.71± 5.02	46.50±5.51
24	59.83±11.00	35.28± 6.60	15.88± 5.81	7.16±2.82
30	74.28± 8.25	37.27± 4.83	27.42± 4.10	9.09±4.34
36	98.13± 5.00	56.38±12.21	32.66±10.22	8.71±3.44
42	144.87±13.31	99.41±12.76	33.75±13.34	11.85±7.24
60	199.07±23.10	162.48±18.33	22.24±10.83	13.00±8.60

* Cells which did not contain large nucleoli were rarely ever seen at the wound edge at any postoperative period studied.
† Standard deviation.

TABLE 2.—*Mitotic Rates of Cells at the Wound Edge in Colchicine-Treated Animals at Various Time Periods After Injury*

Wound Period, Hr.	Cells with Large Nucleoli,* No.	Mitotic Rate/100 Cells	Cells Contributed by Cell Division, No.
12	0.0	0.00±0.00 †	0.00±0.00
24	57.0	0.04±0.08	0.02±0.05
30	58.6	0.19±0.41	0.11±0.24
36	68.0	4.59±2.74	3.12±1.86
42	90.0	5.59 ‡	5.03
48	112.0	8.89±2.77	9.73±3.10
54	136.2	12.67 ‡	17.26
60	161.0	15.58±5.23	25.08±8.42

* Number of cells present at wound edge at the beginning of the eight-hour period of the colchicine inhibition of cell division. Estimated from graph drawn from data in Column 2 of Table 1.
† Standard deviation.
‡ Estimated from graph.

At 24 hours after injury 59.83 cells containing large nucleoli were present per oil-immersion field through all depths of the stroma at the wound edge. They consisted of 35.28 (60.5%) fibroblasts, 15.88 (27.2%) monocytes, and 7.16 (12.3%) corneal stromal cells (total, 58.32). Of the original corneal stromal cells present, 35.28, or 75%, were transformed into fibroblasts by 24 hours after wounding. This is shown by the fact that the corneal stromal cells with large developing nucleoli decreased by 75% between the 12th and 24th postoperative hours. Since the number of corneal stromal cells with large nucleoli remains relatively constant after the 24th postoperative hour, it is assumed that no further transformation of these cells takes place after this time.

(*b*) Colchicine: A steady increase in the number of fibroblasts at the wound edge was found through the time periods studied, 0 to 60 hours (Table 1). No attempt was made to count the cells in incisions older than 60 hours in duration, because the increasing density of cells at the wound edge made accurate counting too difficult. The number of fibroblasts increased from 35.28 at 24 hours to 162.48 at 60 hours after operation.

Counts of mitotic figures in colchicine-treated animals indicated that no measurable cell division occurs during the first 24 postoperative hours (Table 2). Furthermore, no cells resembling fibroblasts could be seen between the limbus and the wound to indicate any possible migration of fibroblasts from limbal tissues. Inasmuch as it can be estimated that at least 10 days would be required for such migration to take place,[3] the migration of fibroblasts per se is eliminated as a source of the fibroblasts found in these wounds.

The role of cell division in providing the increased number of fibroblasts is summarized in Tables 2 and 3.

According to Paletta and Cowdry,[10] the effect of colchicine on mitosis is found within one hour following a subcutaneous injection. For the purposes of calculation of mitotic rates, the effect of colchicine on the cornea is assumed to be eight hours in duration.

The mitotic rates were determined by counting the number of mitotic figures per 100 cells (excluding polymorphonuclear

TABLE 3.—*Fibroblasts Derived from Corneal Stromal Cells at Various Time Periods After Injury*

Wound Period, Hr.	Fibroblasts Formed from Transforming Corneal Stromal Cells	Fibroblasts Contributed by Cell Division of Transformed Corneal Stromal Cells	Total Fibroblasts Expected From Transformation and Cell Division of Corneal Stromal Cells (Running Total)	Tota Fibroblasts Found
0	0.00	--	0.00	0.00± 0.00 *
12	0.55	0.00±0.00	0.55	0.55± 0.55
24	34.73	0.00±0.00	35.28	35.28± 6.60
30	0.00	0.07±0.14	35.35	37.27± 4.83
36	0.00	1.62±0.97	36.97	56.38±12.21
42	0.00	2.07	39.04	79.30 †
48	0.00	3.39±1.08	42.43	99.41±12.76
54	0.00	5.38	47.81	130.50 †
60	0.00	7.45±2.50	55.26	162.48±18.33

* Standard deviation.
† Estimated from graph.

leukocytes), a total of approximately 300 to 600 cells being counted for each time period. From five to seven eyes were counted for each time period studied. Although some of the mitoses definitely appeared to occur in fibroblast-like cells, in general it was impossible to determine the type of cell undergoing division.

Cell division was found to begin between the 30th hour (0.19 mitotic figures/100 cells) and the 36th hour (4.59 mitotic figures/100 cells) after wounding. The mitotic rate reached its maximum at 60 hours, when it was 15.58 mitotic figures/100 cells. Preliminary counts on wounds of 72, 84, 96, and 120 hours indicated that it had decreased by 84 hours (11.70 mitotic figures/100 cells) but had not ended by 120 hours (by inspection). The periods of minimum and maximum mitotic activities found in these experiments agree with the findings of Allgöwer[2] for connective tissue regeneration in rabbit ear wounds.

The results summarized in Tables 2 and 3 indicate that 162.48 fibroblasts per oil-immersion field were found at the wound edge at 60 hours. Of these 35.28 (21.7%) were estimated to have been contributed by the transformation of corneal stromal cells (Table 3, Column 2). The number of fibroblasts which could have arisen by cell division of transformed corneal stromal cells originally present at the wound edge was calculated to be 19.98 (12.3%) (Table 3, Column 3). However, it is not known if these cells newly transformed from corneal stromal cells can undergo cell division. In tissue culture studies of monocytes transforming to fibroblasts, Hulliger found intense mitotic activity in the transforming monocytes and in the early fibroblast-like cells derived from these monocytes but greatly decreased mitosis among fully developed fibroblasts.[11,12]

Thus, it would appear that by the 60th postoperative hour only 55.26 (34.0%) of the 162.48 fibroblasts found could have been contributed by the corneal stromal cells present (Table 3, Column 4). No migration of transformed corneal stromal cells was ever seen. This leaves 107.22 (66.0%) fibroblasts to be accounted for by some other means. In other words, of the total number of fibroblasts present at the wound edge at 60 hours, a maximum of 35% could have been formed from the transformation and division of the original corneal stromal cells and 65% by migration, division, and transformation of cells of an unknown source.

These figures are undoubtedly approximate, but it is obvious that the corneal stromal cells originally present at the wound edge cannot account for the total number of fibroblasts found at the wound edge at 60 hours. Migration of cells of an unknown origin to the wound edge, followed by their transformation to fibroblasts, must occur to account for the total number of fibroblasts actually found at the wound edge.

Mast cells, which were well preserved in this formalin-alcohol-fixed material, were never seen in the corneas of the normal or the wounded eyes, although they were found in large numbers in the limbal tissues. These results agree with those of Wassermann,[13] who found no participation of mast cells in the healing of tendon wounds.

The only other type of cell found at the wound edge, excluding polymorphonuclear leukocytes, was the monocyte. This is in accord with the studies of avascular healing of the corneal stroma by Pullinger and Mann,[14] who found that only polymorphonuclear cells and "wandering" cells entered the cornea from the limbal tissues. Fibroblasts and lymphocytes never entered unless blood vessels invaded the cornea. Pullinger and Mann suggested that these "wandering" cells became transformed into fibroblasts. Maumenee and Kornblueth,[15] using animals injected with trypan blue, have shown the transformation of macrophages to keratoblasts following extensive injuries to the cornea.

In the present studies monocytes were found to be present in various stages of transformation, beginning with the 12th postoperative hour. A series of photomi-

crographs were taken of the various stages of transforming monocytes. These were classified into six stages of transformation approaching the fibroblast. The morphological characteristics of these cell types are summarized as follows.

Stage I. Horseshoe nucleus containing one or more developing nucleoli and only dust-like granular cytoplasm (Fig. 1).

Stage II. Horeshoe nucleus containing very large nucleoli and the first appearance of a lacy cytoplasm (Fig. 2).

Fig. 1.—Stage I transforming monocyte. Two small nucleoli have developed. Giemsa stain; reduced 32% from mag. × 970.

Fig. 2. — Stage II transforming monocyte. Nucleoli are much larger. Giemsa stain; reduced 32% from mag. × 970.

Fig. 3. — Stage III transforming monocyte. Development of basophilic cytoplasm is occurring. Giemsa stain; reduced 32% from mag. × 970.

Stage III. Horseshoe nucleus containing still larger nucleoli and surrounded by a developing lacy cytoplasm. The nucleus is about twice as large as it was in Stage II (Figs. 3 and 4).

Stage IV. Horseshoe nucleus containing very large, well-developed nucleoli and beginning to develop long tails of very basophilic cytoplasm. The nucleus is larger than it was in Stage III cells (Figs. 5 and 6).

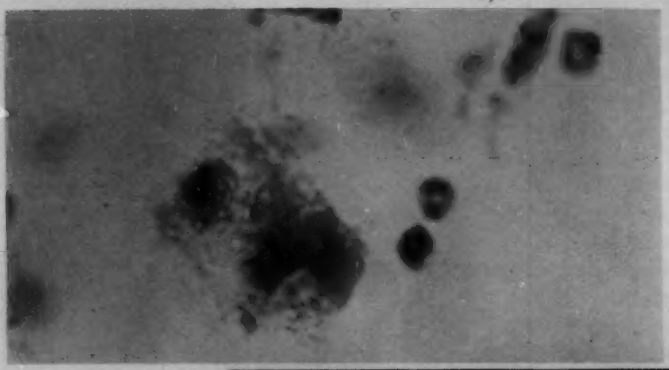

Fig. 4. — Stage III transforming monocyte. Development of basophilic cytoplasm is occurring. Giemsa stain; reduced 32% from mag. ×970.

Fig. 5. — Stage IV transforming monocyte. Cytoplasm has increased in quantity. Giemsa stain reduced 32% from mag. ×970.

Fig. 6. — Stage IV transforming monocyte. Cytoplasm has increased in quantity. Giemsa stain; reduced 32% from mag. ×970.

Fig. 7. — Stage V transforming monocyte. Cytoplasm has become oriented into long tails. Giemsa stain; reduced 32% from mag. × 970.

Stage V. Similar to Stage IV. Two long tails of cytoplasm have developed and each are two to three times as long as the nucleus. Several large nucleoli are present (Figs. 7 and 8).

Stage VI. The horseshoe-type nucleus has begun to elongate and straighten, but some trace of the horseshoe nucleus still remains. At this stage, in some cases, only careful focusing reveals the horseshoe-like remnants of the monocyte-type nucleus. Otherwise the cell is easily mistaken for a fully developed fibroblast—which it may be (Figs. 9 and 10).

The shape of the nucleus, the size of the nucleoli, and the quantity and organization of the cytoplasm were the points which determined the classification of the cell.

These monocytes, in various stages of transformation, were seen in an area extending two or three oil-immersion fields (× 970) away from the wound edge. The greater the distance from the wound edge the less the degree of transformation. Four oil-immersion fields from the wound edge monocytes which had not begun to transform were usually seen. These cells had the monocyte nucleus and dust-like cytoplasm but no nucleoli. Occasionally Stage I monocytes were seen.

It was found useful to group the monocytes of Stages I, II, and III together as early transitional forms and the monocytes of Stages IV, V, and VI together as late transitional forms. Table 4 summarizes the numbers of early and late transitional forms

Fig. 8.—Stage V transforming monocyte. Cytoplasm has become oriented into long tails. Giemsa stain; reduced 32% from mag. × 970.

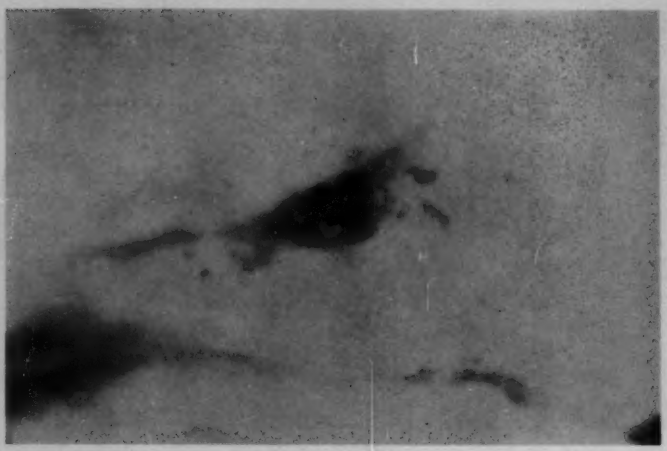

Fig. 9. — Stage VI transforming monocyte. Cell has become fibroblast-like in appearance but still has some traces of monocyte-like nucleus. Giemsa stain; reduced 32% from mag. × 970.

of monocytes found at the wound edge at the various wound periods. The 0-, 12-, 24-, and 30-hour wounds give a clue to the rate of migration and rate of maturation. At zero hours no transitional monocytes of any kind were found. At 12 hours 7.68 early transitional forms were present but no late transitional forms occurred. At 24 hours 6.84 late transitional forms were found. It would seem plausible that these were supplied by the 7.68 early transitional forms seen at 12 hours. If it is assumed that the late transitional forms of each time period contribute during the next time period to the number of fibroblasts counted at the wound edge, a total of 73.85 monocytes would appear to be transformed to fibroblasts by 60 hours. This figure is arrived at by summation of the total number of late transitional forms found at each time period from 0 to 54 hours, inclusive (Table 4, Column 3).

Fig. 10. — Stage VI transforming monocyte. Cell has become fibroblast-like in appearance but still has some traces of monocyte-like nucleus. Giemsa stain; reduced 32% from mag. × 970.

TABLE 4.—*Differential Count of Transforming Monocytes at the Wound Edge at Different Time Periods After Injury*

Wound Period, Hr.	Monocytes, Stages I, II, III	Monocytes, Stages IV, V, VI
0	0.00±0.00 *	0.00±0.00
12	7.68±4.97	0.00±0.00
24	9.03±5.58	6.84±3.66
30	19.62±2.61	7.70±2.18
36	17.80±6.10	15.16±5.11
42	18.15 †	15.60 †
48	18.30±4.81	18.46±8.90
54	15.05 †	13.00 †
60	12.20±4.22	10.05±9.81

* Standard deviation.
† Estimated from graphs.

According to these estimations, the 162.48 fibroblasts seen at the wound edge at 60 hours arose as follows: 35.28 (20.9%) were

TABLE 5.—*Analysis of Sources of Fibroblasts at Various Time Periods After Injury*

Wound Period, Hr.	Actual No. of Fibroblasts	Fibroblasts Formed from Transforming Corneal Stromal Cells	Fibroblasts Formed from Cell Division	Fibroblasts Formed from Transforming Monocytes	Theoretical Total No. of Fibroblasts
0	0.00±0.00 *	--	--	--	0.00
12	0.55±0.85	0.55±0.85	0.00±0.00	0.00±0.00	0.55
24	35.28± 6.60	34.73	0.02±0.05	0.00±0.00	35.30
30	37.27± 4.83	0.00	0.11±0.24	6.84±3.66	42.25
36	56.36±12.21	0.00	3.12±1.86	7.79±2.18	53.16
42	79.00 †	0.00	5.03	15.16±5.11	73.35
48	99.41±12.76	0.00	9.73±3.10	15.60	98.68
54	130.50 †	0.00	17.26	15.46±8.90	131.40
60	162.48±18.33	0.00	25.08±8.42	13.00	169.48

* Standard deviation.
† Estimated from graph.

Fig. 11.—Neutral red vital staining. Zero-hour wound. Wound edge. One small cell is stained. Reduced 32% from mag. × 430.

formed from transformation of corneal stromal cells; 19.98 (11.8%), from cell division of these transformed corneal stromal cells; 73.58 (43.5%), by transformation of monocytes to fibroblasts, and 40.37 (23.9%), by division of the newly formed fibroblast-like cells derived from monocytes (total, 169.21).

The breakdown of the contribution of these various sources of cells to the total number of fibroblasts found is summarized in Table 5.

Fig. 12.—Neutral red vital staining. Zero-hour wound. One field from wound edge. No cells are stained. Reduced 32% from mag. × 430.

Fig. 13.—Neutral red vital staining. Twelve-hour wound. Wound edge. Numerous cells are stained (many at different depths of focus and are seen as dark shadows). Reduced 32% from mag. × 430.

Neutral Red Preparations.—In order to evaluate further the role of transforming monocytes in supplying the wound with fibroblasts, studies were undertaken with use of neutral red vital staining. Monocytes and macrophages take up large quantities of this dye, and fibroblasts, little or none.

Under the conditions of these experiments the corneal stromal cells of normal corneas did not take up the neutral red. An occasional cell, round in shape, took up large quantities of the dye (Figs. 11 and 12). The numbers of these cells amounted to about one in each high-power field (× 430).

Twelve hours after wounding, large numbers of cells throughout the cornea took up the dye (Figs. 13 and 14). Counterstaining with methylene blue to reveal the nucleus and nucleoli showed that *all* the corneal stromal cells throughout the cornea had taken up the dye similarly to macrophages. The uptake of dye was even more intense 24 hours after wounding (Figs. 15 and 16). The fibroblast-like cells of the wound edge, which contained the large nucleoli as revealed with methylene blue, also took up the dye intensively.

Thirty-six hours after wounding, however, a new phenomenon occurred. Some of the fibroblasts of the wound edge took up no neutral red at all, although a large number of them did (Fig. 17). The cells away from the wound edge continued to take up the dye intensively (Fig. 18).

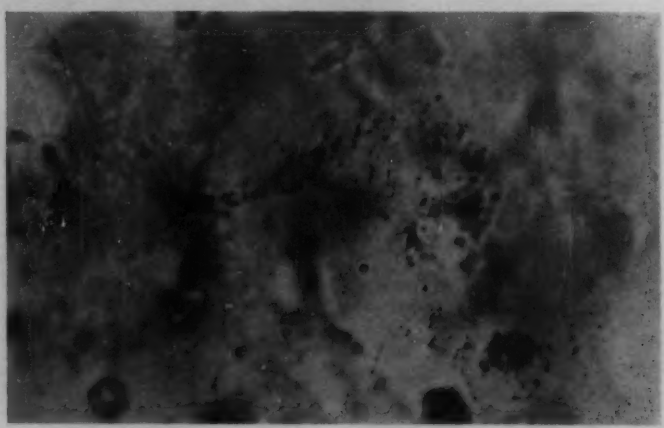

Fig. 14.—Neutral red vital staining. Twelve-hour wound. One field from wound edge. Numerous cells are stained. Reduced 32% from mag. × 430.

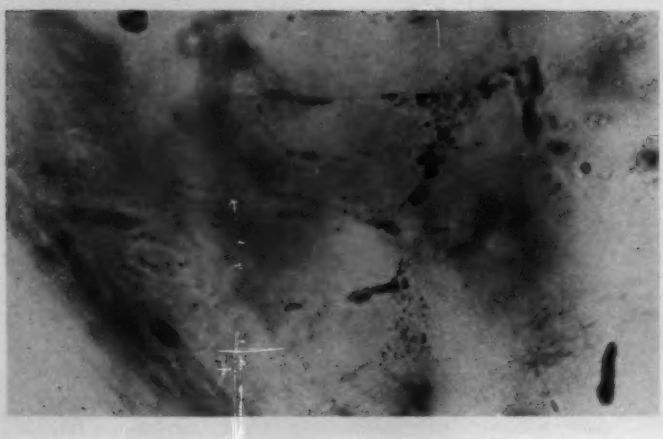

Fig. 15. — Neutral red vital staining. Twenty-four-hour wound. Wound edge. Numerous cells continue to take up stain at wound edge. Reduced 32% from mag. × 430.

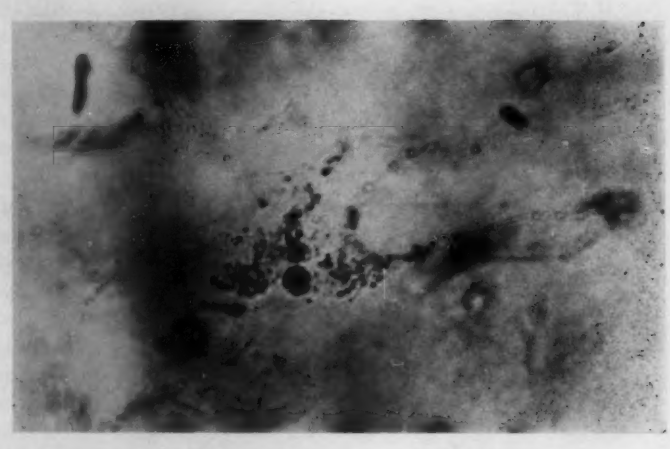

Fig. 16.—Neutral red vital staining. Twenty-four-hour wound. One field from wound edge. Cells continue to take up stain. Reduced 32% from mag. × 430.

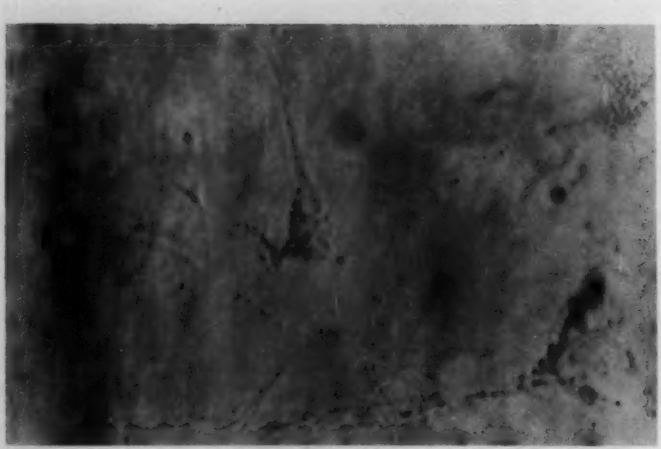

Fig. 17.—Neutral red vital staining. Thirty-six-hour wound. Wound edge. Wound edge cells continue to take up stain. Reduced 32% from mag. × 430.

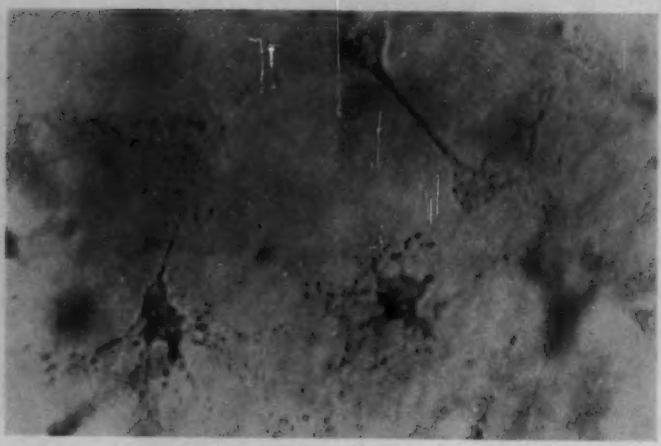

Fig. 18.—Neutral red vital staining. Thirty-six-hour wound. One field from wound edge. Numerous vitally stained cells are found. Reduced 32% from mag. × 430.

Fig. 19.—Neutral red vital staining. Forty-eight-hour wound. Wound edge. Vitally stained cells occur in decreasing numbers. Reduced 32% from mag. × 430.

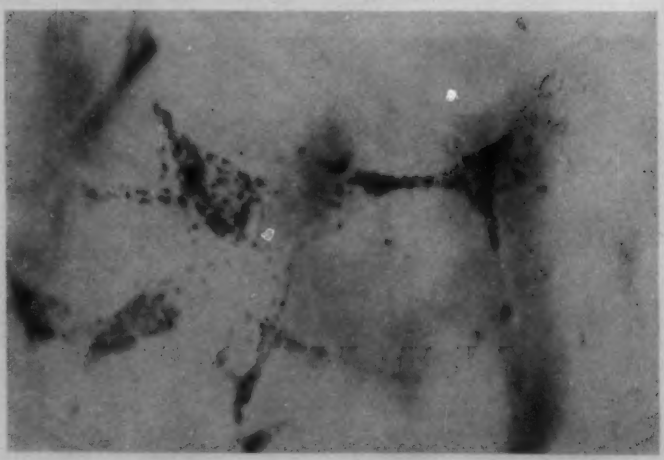

Fig. 20.—Neutral red vital staining. Forty-eight-hour wound. One field from wound edge. Numerous vitally stained cells are found. Reduced 32% from mag. × 430.

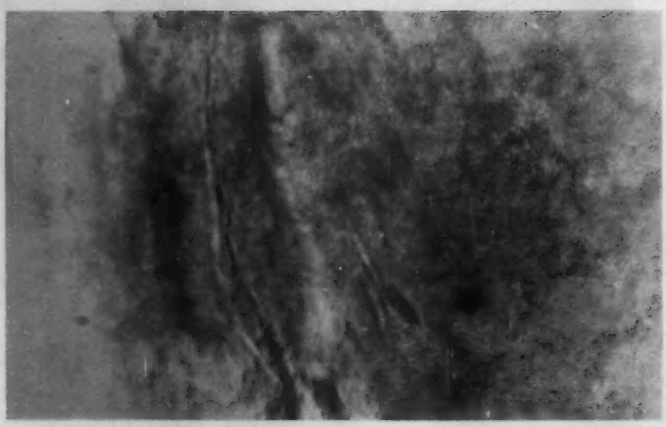

Fig. 21.—Neutral red vital staining. Sixty-hour wound. Wound edge. No neutral red-positive cells are to be found. Reduced 32% from mag. × 430.

Forty-eight hours after injury an increasing proportion of fibroblasts at the wound edge failed to take up the dye, although many neutral red-positive fibroblasts were still seen (Fig. 19). The cells away from the wound edge continued to take up the dye as usual (Fig. 20).

At 60, 72, 84, and 96 hours after wounding a very striking neutral red-negative area bordering the wound edge was seen (Fig. 21). Counterstaining with methylene blue revealed that this area was filled with fibroblasts. However, the cells away from the wound edge continued to take up the dye (Fig. 22), although the reaction became definitely less intense by 84 and 96 hours.

Similar results were seen when trypan blue was used instead of neutral red, but, since this dye photographs relatively poorly in black and white, the studies were continued only with neutral red.

The results with neutral red were interpreted as follows: Within 12 hours after wounding an unknown injury factor released by the wound reaction causes the transformation of all the corneal stromal cells to macrophage-like cells. These continue to behave physiologically like macrophages until at least 72 to 96 hours after wounding. This is in keeping with the findings of Chevremont,[16] who has found that following injury all cells in the injured

Fig. 22.—Neutral red vital staining. Sixty-hour wound. One field from wound edge. Cells away from wound edge continue to take up the stain. Reduced 32% from mag. × 430.

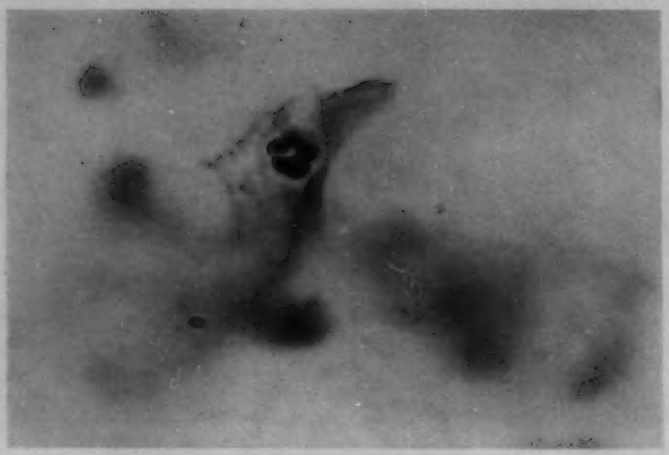

Fig. 23.—Corneal stromal cell phagocytosing polymorphonuclear leukocyte. Thirty-six-hour wound. Midway between limbus and wound edge. Giemsa stain. Reduced 32% from mag. ×970.

area, regardless of origin, are transformed into physiological macrophages which phagocytize trypan blue. He has shown that traces of choline are capable of producing this transformation in tissue cultures of various cell types.

It is significant to note in this connection that in the Giemsa-stained preparations the corneal stromal cells from the limbus to the wound edge were found to be phagocytosing polymorphonuclear leukocytes (Fig. 23). During the early wound periods (up to about 48 hours) the fibroblasts were also found to be phagocytosing polymorphonuclear leukocytes (Fig. 24).

The results of the experiments presented in this paper suggest at least two different "transforming" factors may be released by the wound reaction: one which acts over a considerable distance and which transforms all of the corneal stromal cells to macrophage-like cells and one which acts only in a very limited area and which transforms macrophages, derived from either corneal stromal cells or monocytes, at the wound edge into fibroblasts.

Ebert and Florey [17] found that activated macrophages formed from preexisting histiocytes did not migrate toward an injured area although macrophages newly developed

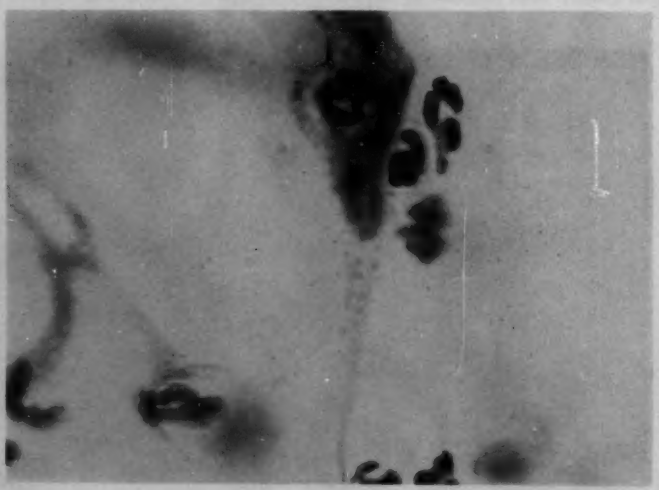

Fig. 24.—Fibroblast phagocytosing polymorphonuclear leukocyte at wound edge. Thirty-six-hour wound. Giemsa stain. Reduced 32% from mag. ×970.

from monocytes did. If this observation holds for the activated macrophages of the cornea, then the macrophage-like cells contributing to the increased numbers of fibroblasts at the wound edge must be derived from (1) those originally present at the wound edge and (2) those derived from cells still capable of migrating, e. g., the monocytes. These conclusions are supported by the data on cell counts and transformations of monocytes presented in Tables 4 and 5. The number of corneal stromal cells with large nucleoli at the wounded edge was found to remain relatively constant from 24 hours on (Table 1), and it is assumed that there is no further transformation of these cells after 24 hours. This assumption is based on the finding in these experiments that the corneal stromal cells transform to macrophage-like cells and the finding by Ebert and Florey [17] that activated histiocytes do not migrate toward an injured area.

It has been known for many years that the morphological characteristics of monocytes and fibroblasts in tissue culture depend on the nutrient medium.[18] Fibroblasts grown in tissue culture in which the nutrient medium is similar to serum become monocyte-like in appearance. Monocytes grown in culture in fluid supplemented with protein breakdown products become fibroblast-like in appearance. Such protein breakdown products are known to be produced by the injury of tissues.[19-22]

Hulliger [11] has recently demonstrated the transformation of monocytes to fibroblasts in tissue culture under controlled and reproducible conditions. Hulliger, James, and Allgöwer [23] have shown significant production of hydroxyproline by fibroblasts derived from monocytes in these tissue cultures. Hydroxyproline is one of the main constituents of collagen and is considered to be a specific product of fibroblast activities. This work of Hulliger, James, and Allgöwer provides proof that monocytes are capable of transforming into fibroblasts and producing collagen components. For a general discussion of this problem, with a historical review and the presentation of original quantitative data, the reader is referred to the monograph, "The Cellular Basis of Wound Repair," by Allgöwer [2] and also to the work of Hartwell.[24]

The recent discovery of adaptive enzymes [25] has led to the finding that monocytes, under different environmental conditions, may synthesize enzymes for which they were previously (as in the blood stream) either negative or relatively negative.[26,27] Especially pertinent to studies on wound healing is the finding that monocytes in the process of transforming to giant cells or epithelioid cells develop a positive, saliva-resistant periodic acid-Schiff reaction.[26] This finding is usually accepted as positive evidence for the presence of mucopolysaccharides. Cultures of fibroblasts synthesize large quantities of mucopolysaccharides,[28] and any cell which is to become a fibroblast must possess the potential for synthesizing mucopolysaccharides.

A number of questions are posed by the results of these experiments: What is the nature of the factor which causes the transformation of the corneal stromal cells to macrophages? Is it choline? If so, what is its source in the wound reaction? What is the stimulus which causes the transformation of cells at the wound edge into fibroblasts? What kinds of enzymes are to be found in the newly developed cytoplasm of these fibroblasts? Do these cells synthesize a whole new enzyme apparatus for the production of collagen and mucopolysaccharides?

Summary

The normal pattern of healing as studied in whole mounts of the corneal stroma is quantitatively described. The corneal stromal cells at the wound edge transformed into fibroblasts within the first 24 hours after injury. The site of this transformation was a narrow border about 200μ wide on each side of the wound edge.

Quantitative counts of the various cell types present at the wound edge indicated

that approximately 75% of the corneal stromal cells originally present at the wound edge were transformed into fibroblasts during the first 24 postoperative hours. The remaining 25% did not appear to transform.

Cell division, as estimated in colchicine-treated animals, began between the 30th and 36th postoperative hours and reached a peak at 60 hours after injury. Although mitosis decreased to about one-half the maximum by 84 hours, it had not ceased by 120 hours after injury.

It was estimated that, of the total number of fibroblasts found at the wound edge at 60 hours, approximately 35% were derived from the transformation and division of the corneal stromal cells originally present at the wound edge and 65%, from the migration, transformation, and division of monocytes. Mast cells were never seen in the normal or wounded corneas but did occur in large numbers in the limbal tissues.

Numerous monocytes with developing nucleoli and cytoplasm were found at the wound edge, beginning with the 12th postoperative hours. These were found to be in various stages of transformation from ordinary monocytes to forms which could be differentiated from fibroblasts only with difficulty. These monocytes were found to undergo transformation only at the wound edge or a short distance from it—that is, two or three oil-immersion fields (× 970). Only early transforming cells occurred at 12 hours, but both early and late stages occurred by the 24th postoperative hour. On the basis of the rate of appearance of these transforming monocytes at the wound edge and the rate of their maturation, it was estimated that these cells accounted for 65% of the fibroblasts found at the wound edge at 60 hours after injury.

In order to evaluate further the role of the monocyte in wound healing, vital staining of whole corneas denuded of epithelium was undertaken. Stromal cells of normal corneas did not take up the dye under the conditions of these experiments. Within 12 hours after injury *all* the corneal stromal cells became transformed to macrophage-like cells and transported the dye. The cells which transformed to fibroblasts at the wound edge were filled with neutral red vacuoles during the early postoperative hours but differentiated later to forms which could no longer transport the dye. By the 60th postoperative hour a completely negative neutral red zone bordering the wound edge was found but the cells away from the wound edge continued to take up the dye. Counterstaining with methylene blue showed that this neutral red-negative zone was filled with fibroblasts.

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Radiography of Aqueous Humor Outflow

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Important details of the aqueous humor outflow system, previously inaccessible to study in the intact eye, can now be observed by radiography. The technique is based on radiographs of the angle of the anterior chamber taken after replacing aqueous humor with water-soluble radiopaque material.

Biomicroscopy is limited as a tool for the study of the crucial details of the mechanism of aqueous humor outflow. A gonioscopic view of the angle of the anterior chamber reveals the trabecular meshwork, which is only the beginning of the outflow system. And with the slit lamp the aqueous veins and laminary veins, beneath the conjunctiva, can be identified and traced in a retrograde direction to the point where they disappear into the sclera. The system of minute drainage channels, between the inner trabecular and outer episcleral surfaces, within the optically opaque sclera, and beyond the limits of biomicroscopy, has been studied by two major research methods. The use of serial sections of the tissues of the angle of the anterior chamber culminated in the work of Theobald.[1] There have been many studies employing intracameral injection of a foreign material to delineate the outflow channels. The use of the neoprene cast method in ocular tissues by Ashton[2,3] was an important recent modification of this approach. Ashton[2] mentions the distortion of anatomic details inherent in methods depending on histological sections. Although Ashton's method is an ingenious one, it involves total disruption of the normal physiologic anatomy.

Early in the work[4] on radiography of the aqueous outflow mechanism a thorough study was made of the effects on the rabbit eye of replacement of aqueous with water-soluble radiopaque materials. Multiple slit-lamp examinations of each eye in that series and subsequent histological study revealed only a mild and transient response of the anterior segment to such contrast media. Radiography is by far less damaging to the delicate ocular tissues than those methods employing histological sections or neoprene casts. This new technique does not respect the normal physiology to the ideal degree of biomicroscopy, but it is not limited to the visible surfaces. Radiography permits the investigator to study a functioning and essentially intact aqueous outflow system, particularly within the depths of the sclera.

Replacement and Refined Roentgenographic Techniques

In the present experiment 0.2 cc. of 50% sodium diatrizoate (Hypaque Sodium 50%, Winthrop-Stearns) was used to replace the same volume of aqueous. The technique employed was identical to that described in the preliminary report,[4] with the following exceptions: The rabbits were placed in a lateral position for the filming; depth of anesthesia was more carefully controlled, and restraints, which in no way exerted pressure on either neck or eye, were used.

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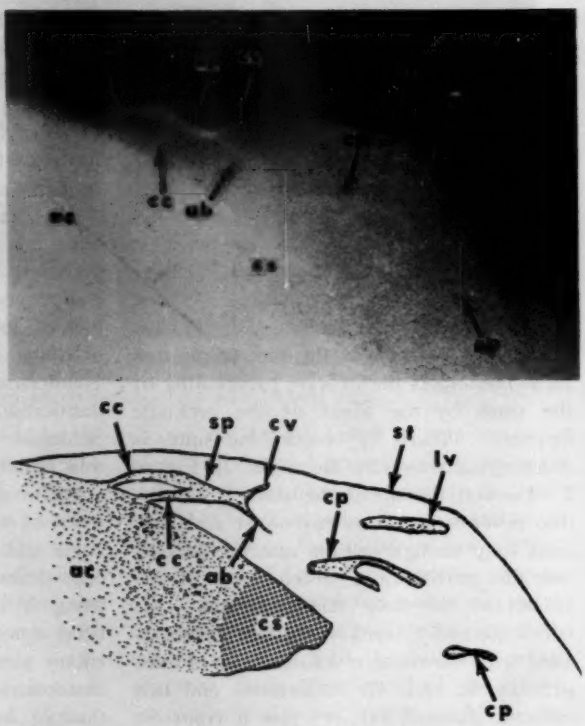

Fig. 1.—(*ac*) Angle of anterior chamber; (*ab*) anastamotic branch; (*cc*) collector channel; (*cp*) vein of ciliary plexus; (*cs*) tip of ciliosclerał sinus; (*cv*) communicating vessel; (*lv*) laminary vein; (*sp*) vessel of deep scleral plexus; (*st*) scleral tissue edge.

All radiographic exposures were taken within 20 minutes of replacement of aqueous by the contrast solution. Kodak Medical X-Ray Film and the usual medical film developer were used for most of this study. A few radiographs were taken on the much slower, finer-grained industrial x-ray film, Ansco Superay 'A,' and developed with fine-grain developer, DK-20.

A specially constructed experimental x-ray tube, of the type designed by Ehrenberg and Spear,[5] was used to obtain all of the films reproduced here with the exception of Figure 2. This apparatus contains a fine focus of 25μ. This is a stationary-focus system which employs electrostatic focusing, thus avoiding the complicated power unit needed in the earlier fine-focus tubes employing magnetic focusing. The machine was set at 34 kv. and 200 ma. for all exposures. The tube-to-object distance was varied from 4 to 11 in., and the exposure time, from one to eight minutes, depending on the intensity of the beam and the type of film being used. Detailed radiologic factors for each exposure are of little value, since the intensity of the x-ray beam varied with the humidity as it affected the efficiency of the cooling apparatus. Contrary to the conventional x-ray tube design, the anode is cooled by a slow stream of carbon tetrachloride. The circulating system consists of a small centrifugal pump and a reservoir; the connections are made with flexible plastic tubing.

The Pathways of Aqueous Outflow

The modern concept of the aqueous outflow system in the rabbit is based on the foundation provided by the studies of Troncoso and Castroviejo [6] and Troncoso.[7] They describe in the rabbit a cleft, the ciliosclerał sinus, which is situated between the sclera and the outer side of the ciliary body and communicates with the anterior

chamber. This sinus corresponds to the canal of Schlemm in man.

Figure 1 is an enlargement of a roentgenogram of the angle of the anterior chamber of a rabbit eye taken with the 25μ focus tube a few minutes after replacing 0.2 cc. of aqueous with the same volume of sodium diatrizoate. This radiograph of the eye reveals three of the most important details of the aqueous drainage system. First, the tip of the cilioscleral sinus (*cs*) is visible. In many of the films the intense contrast of the radiopaque material obliterates the delicate partitioning of the sinus by the fibers of the pectinate ligament. Where this occurs the sinus is indistinguishable from the angle. In Figure 1, however, the tip of the sinus is thrown into relief where it is narrowest and contains only enough opaque material to outline this partitioning. Second, one of the vessels of the deep scleral plexus (*sp*), which normally contains aqueous, here is filled with the contrast solution and is seen, partially on end. At its anterior end two collector channels (*cc, cc*) join it from the anterior portion of the cilioscleral sinus. At its opposite end are two additional branches. One is an anastomotic branch (*ab*) carrying the fluid from the deep scleral plexus laterally toward the ciliary body. The other is a communicating vessel (*cv*) extending up toward the episclera. Third, still more lateral to the angle, in the region of the ciliary body, are observed three vessels which are seen for only a short portion of their courses. The lower two are vessels of the ciliary venous plexus (*cv, cv*) which contain radiopaque solution from the anterior chamber. The upper vessel, a laminary vein (*lv*), is at or near the scleral surface and is transporting the contents of the ciliary venous plexus.

This radiograph demonstrates two systems of aqueous drainage: the classical pathway, from the deep scleral plexus by communicating vessels to the episcleral plexus, and another pathway into a plexus of veins in the ciliary muscle. Although Henderson [8] first described the direct communication in man between the canal of Schlemm and the anterior ciliary veins, this finding was neglected by most subsequent investigators. Kiss [9] described a network of veins in the ciliary body near the angle and proposed this as a second aqueous drainage system. Weinstein,[10] also using histological sections, traced superficial aqueous-containing vessels back to the ciliary plexus of veins and, virtually alone, championed this double-drainage-system theory. Ashton [11] has now tended to confirm this second outflow mechanism on the basis of his work with neoprene. The size of these vessels in Figure 1 agrees with their histological descriptions, and their lack of sharp definition is probably due not only to their location within the thickness of the ciliary mass but also to their function as blood- as well as aqueous-containing vessels. The modern concept of this double system in man has probably been

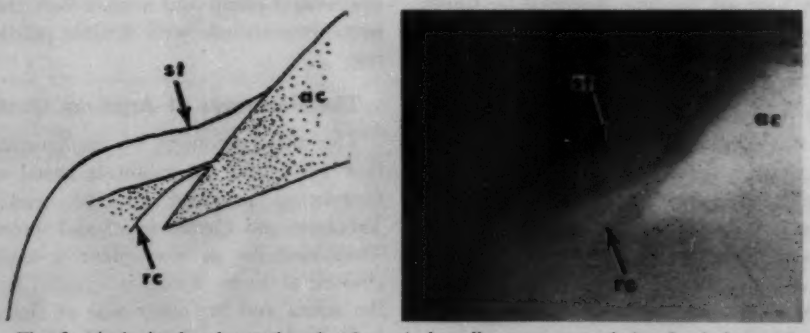

Fig. 2.—(*ac*) Angle of anterior chamber; (*rc*) radiopaque cone; (*sl*) scleral tissue edge.

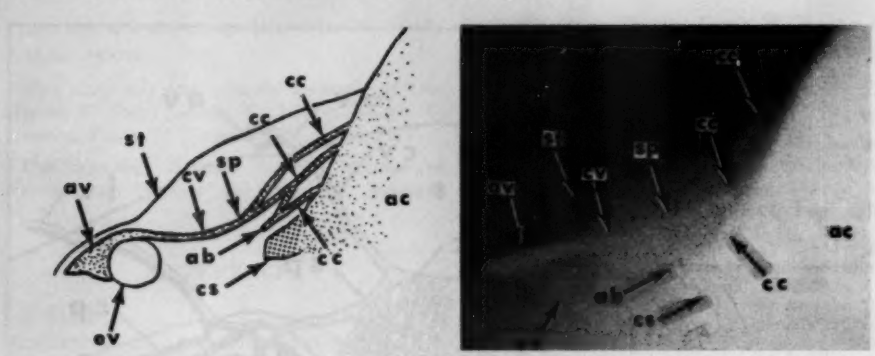

Fig. 3.—(*ac*) Angle of anterior chamber; (*ab*) anastamotic branch; (*av*) aqueous vein; (*cc*) collector channel; (*cs*) tip of ciliioscleral sinus; (*cv*) communicating vessel; (*ev*) episcleral vein; (*sp*) vessel of deep scleral plexus; (*st*) scleral tissue edge.

stated most succinctly by Duke-Elder [12]: "The whole system can be resolved into three components. From out of the eye, issuing from the ciliary venous plexus which lies in the ciliary muscle, there emerges a considerable number of ciliary efferent veins carrying blood. From the canal of Schlemm there also issues a large number of efferent vessels carrying aqueous. These two systems become inextricably mixed in the deep scleral plexus, whence numerous channels emerge on to the surface of the sclera. There they empty into the subconjunctival veins."

Figure 2 is the only one of these radiographs taken with a 2 mm. focal spot tube. It is included to demonstrate the marked reduction in detail of the drainage system which is inherent in the techniques using conventional diagnostic x-ray tubes. The radiopaque cone (*rc*) within the sclera should not be attributed to aqueous veins filled with contrast material. The preceding and subsequent films demonstrate the resolution of such a cone into a number of the channels of the initial outflow system: the individual collector channels, vessels of the deep scleral plexus, and communicating vessels. Aqueous veins, then, are those vessels observed with the slit lamp which originate from the depths of the sclera, contain only aqueous, run beneath the conjunctiva, and empty into blood-containing episcleral vessels. Laminary veins differ from aqueous veins in that they contain a visible column of blood as well as aqueous even as they emerge from the sclera.

In Figure 3 the fine-focus tube resolves what would be a cone with the earlier method into the radiographic shadows of three separate collector channels (*cc, cc, cc*). All three anastomose. From this plexus (*sp*)

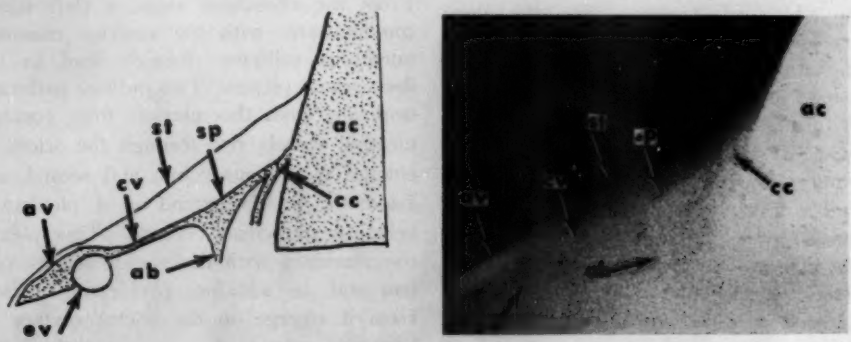

Fig. 4.—Same as Figure 3.

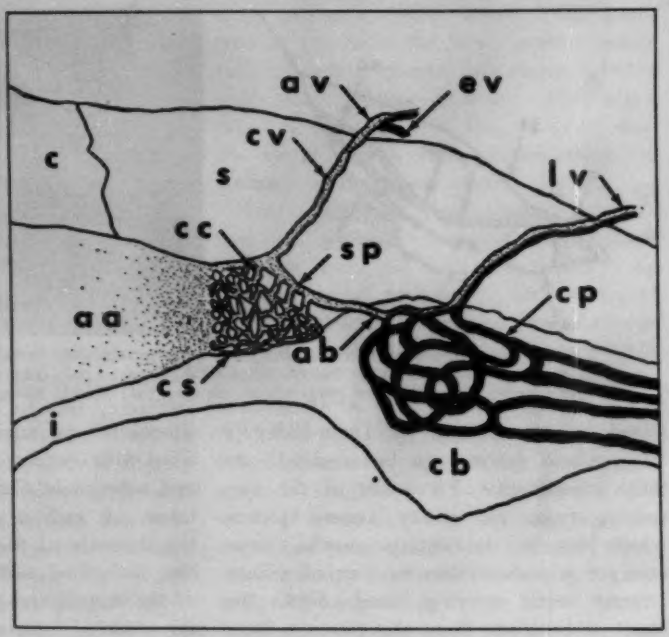

Fig. 5.—(*c*) Cornea; (*s*) sclera; (*i*) iris; (*cb*) ciliary body; (*aa*) angle of anterior chamber; (*ab*) anastamotic branch; (*av*) aqueous vein; (*cc*) collector channel; (*cp*) ciliary venous plexus; (*cs*) cilioscleral sinus; (*cv*) communicating vessel; (*ev*) episcleral vein; (*lv*) laminary vein; (*sp*) vessel of deep scleral plexus.

there is a communicating vessel (*cv*) to the scleral surface, where it joins a much larger vessel which contains the contrast material and is seen on end. This larger vessel is accompanied by a blood-containing vessel, and, if it were seen with the slit lamp, would be called an aqueous vein (*av*) traveling side by side with an episcleral vein (*ev*) prior to their actual confluence.

The angle in Figure 4 reveals a single collector channel (*cc*) with the water-soluble contrast material flowing through it into a vessel of the deep scleral plexus (*sp*). Two additional vessels enter the deep scleral plexus near this point. They are transmitting fluid from either the ciliioscleral sinus to the plexus or from the plexus back through the sclera to enter the ciliary drainage system. From the deep plexus a communicating vessel (*cv*) (these are considerably less numerous than the collector channels) travels through the sclera to the surface, where its radiopaque contents can be seen pouring into a large vessel (*av*) which has a blood-containing vein (*ev*) beside it.

Figure 5 is a diagramatic representation of the pathways of aqueous humor outflow in the rabbit. It is based on the figure of Troncoso [7] and is modified to conform to those details of the schema for the human eye [8,10,12] which the present study has demonstrated by means of radiography.

Summary

A number of anatomic details of the aqueous outflow system in the living rabbit eye are demonstrated by radiography. From the ciliioscleral sinus, a cleft which communicates with the anterior chamber, numerous collector channels lead to the deep scleral plexus. Two outflow pathways originate from this plexus: first, communicating vessels rise through the sclera to emerge as aqueous veins; and second, anastomotic vessels extend to a plexus of veins in the ciliary muscle. This plexus communicates with the vortex venous system and, in addition, perforating vessels from it emerge on the scleral surface as laminary veins. Aqueous and laminary

veins are tributaries of the anterior ciliary venous system.

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Incorporation of S^{35} in Healing Wounds in Normal and Devitalized Corneas

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In a recent report [1] on the responses of the ocular tissues to injury an analysis was made of the role the various components of connective tissue play in wound repair. These studies, which clearly indicate the importance of the initial events, aroused further interest in the nature of these responses. With suspicion that the normal cell constituents of connective tissue adjacent to an injury play a vital part in repair, the healing of wounds in normal and devitalized corneas was investigated. The purpose of this study is twofold: to evaluate the importance to healing of those cell constituents at the edge of a fresh wound and to describe the time and site of formation of sulfated mucopolysaccharides in a cornea recovering from injury.

Methods

Maumenee's [2] method of killing corneal cells by freezing was used because it is believed this technique does not directly degrade the chemical constituents of the fibers or ground substances. However, there is little doubt that, during freezing and thawing, minute ice crystals may disrupt the arrangement of the collagen fibrils, and during the postfreezing period destruction of chemical constituents may, and probably does, occur at a rate greater than normal.

Seventy Dutch rabbits were used. Under pentobarbital (Nembutal) and topical tetracaine anesthesia, the right cornea of each rabbit was frozen by application of a conical copper cup filled with 70 ml. of solidified carbon dioxide (Dry Ice)-alcohol mixture (−72 C) to the cornea for one minute. The round 6 mm. in diameter tip of the cup was concave, curved to fit the rabbit's cornea. Owing to the high conductivity and thinness of the copper tip, it is believed that the cornea was frozen quickly and held at a very low temperature for the time of application. It was demonstrated histologically that this method killed all the cells in the frozen area. Upon removal of the cup, the cornea thawed immediately, and a perforating vertical keratome incision 2 mm. in length was made in the center of the previously frozen area. (In a few cases incisions of 4 mm. were also studied.) An identical incision was made in the left eye, which had not been frozen. No sutures were used. The animals were killed at from 1 to 22 days later, and, in addition, one each was studied at 35 and at 45 days. The eyes were fixed in 4% lead acetate in 8% formol or Carnoy's solution, and sections were cut at right angles to the incision.

The reticular connective tissue fibers which form early in regeneration were studied with the aid of Wilder's silver technique. Identification of various cell types was made in the usual hematoxylin and eosin preparations. The periodic acid-Schiff (PAS) reaction was employed because of its affinity for the carbohydrate

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moiety associated with the fibers (Glegg[3]), and the metachromatic reaction with toluidine blue, because it demonstrates the presence of connective tissue mucopolysaccharides, both sulfated and nonsulfated types.

The use of radioautographs permits the visualization of the place, time, and approximate quantity of synthesis of new sulfated mucopolysaccharides. By indicating their rate of formation, this technique supplements the information given by metachromatic staining, which shows merely the presence of mucopolysaccharides. One millicurie of S^{35} as Na_2SO_4 per kilogram of body weight was injected intravenously seven hours before autopsy. These eyes were fixed in Carnoy's solution, and paraffin sections were stained with hematoxylin. Sections were then coated, as described by Gross et al.,[4] with bulk emulsion, Ansco A. The reduction of silver particles in the emulsion indicated the presence of organically bound sulfate in the underlying tissue. Boström and Mansson[5] have shown that S^{35}-labeled inorganic sulfate is incorporated almost exclusively in the mucopolysaccharide component of connective tissue. Moreover, any remaining traces of unbound inorganic sulfate remaining in the body seven hours after an intravenous injection would be washed out during preparation of the sections prior to staining.

Results

Healing of Incisions in Normal Corneas. Twenty-four hours after an incision was made in the normal cornea, glycogen-filled epithelial cells had covered the wound completely. In several cases the cells had formed a plug in the cut, whose edges were held together by a fibrin clot. Although a few cells were generally present, in some cases no keratoblasts were found adjacent to the cut. This was especially noticeable in the posterior regions. It appeared as if those cells which had been injured directly by the incision had disappeared from a narrow zone along the wound edge. Very few polymorphonuclear leukocytes were seen at either the 24- or the 48-hour stage (these were the pseudoacidophils characteristic of the rabbit), and still fewer were found by the 7th day, when the remaining polymorphonuclear leukocytes had the usual appearance of neutrophils. Cells clearly of the macrophage type were very infrequent. No obvious fiber formation occurred during the first two days. A concentration of enlarged keratoblasts, which was greatest immediately beneath the epithelial plug, was seen along the margins of the 48-hour incision. The possibility that fibrillogenesis had taken place was checked by the use of Wilder's reticular connective tissue stain. At the 24-hour stage, only one case was found in which new reticular fibers had been formed. These fibers stained characteristically, but they were short and confined to the area immediately under the epithelium. By the 48-hour stage, however, argyrophilic fibers were found in most cases. When present, they were always in the anterior portion of the incision, at the interface between the epithelium and the stroma (Fig. 1). The PAS method, which stains the cornea strongly, was not affected by the incision. On the contrary, the metachromatic reaction was often altered by a reduction in intensity in an area immediately adjacent to the cut, especially in the posterior portions. This change in metachromasia has been described by Aurell,[6] who attributed it to swelling of the corneal stroma. Although some swelling was observable in these incisions, it is believed that the reduction in metachromasia can be better correlated with the deficiency of cells than with the edema.

Radioautographs of early stages were very informative. In all cases with no cells at the wound edge, no incorporation of S^{35} occurred from the 17th to the 24th hour after injury in a narrow zone immediately adjacent to the cut. In others, incorporation of radioactive sulfate in the stromal tissue was normal up to the margin of the wound. In two of the four cases examined at the 24-hour stage, and in all cases by

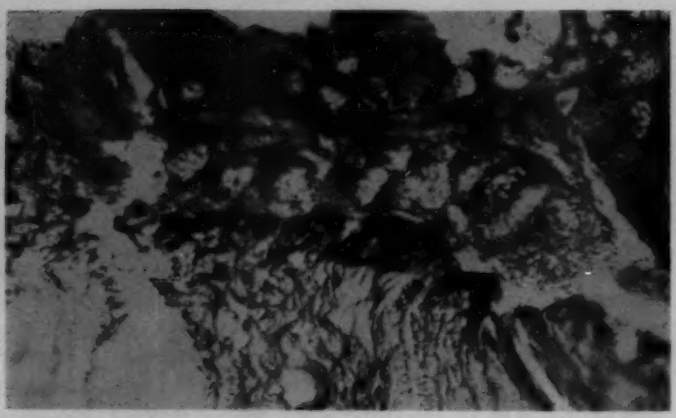

Fig. 1.—First formation of reticular fibers in a 24-hour wound made in a normal cornea. Notice their close relationship with the epithelial cells.

48 hours (Fig. 2), it was obvious that in an extremely narrow band on the wound surface radioactive sulfate was being laid down in an organic form at a rate greater than normal. This observation indicates that synthesis of sulfated mucopolysaccharides is the first sign of new connective tissue formation. It precedes, by a short interval, the first appearance of the reticular fibers. Therefore, the first steps in the formation of new ground substance, at a rate above that required for normal maintenance, can be shown to begin as early as the 17th to 24th hours. This demonstration of active sulfate incorporation may be correlated with the aggregation of enlarged stromal cells at the wound edge. The steps leading up to this fibroblast concentration have been investigated by Weimar.[7] She has shown that a zone of cells 200μ in width bordering an incision become structurally and physiologically changed very soon after the wound has been made. This band of modified corneal cells coincides with the area of increased S^{35} uptake found in the present study.

Healing as indicated by reticular fiber formation was found to be well established in all cases by the fifth day. The polymorphonuclear leukocytes were less evident, but a few lymphocytes were then seen. Many stromal fibroblasts were found at the wound edge and in the new connective tissue. This tissue formed a considerable mass in the anterior part of the incision and consisted essentially of basophilic

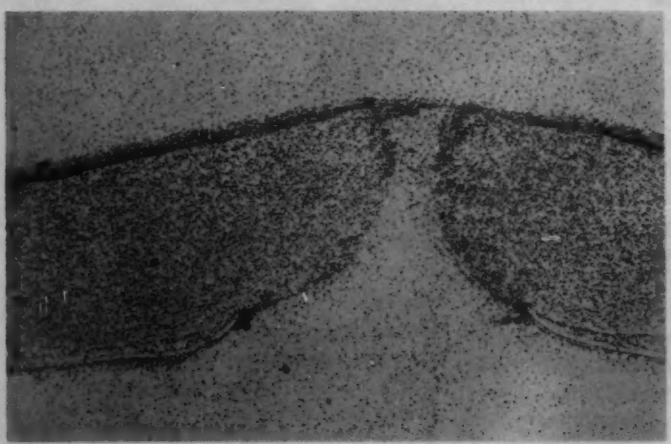

Fig. 2.—Radioautograph of a normal corneal wound on the second day of healing. The entire cornea is synthesizing sulfate at a normal rate, but the rate at the edges of the cut is higher than normal, as indicated by the increased density of silver granules in the emulsion over this region.

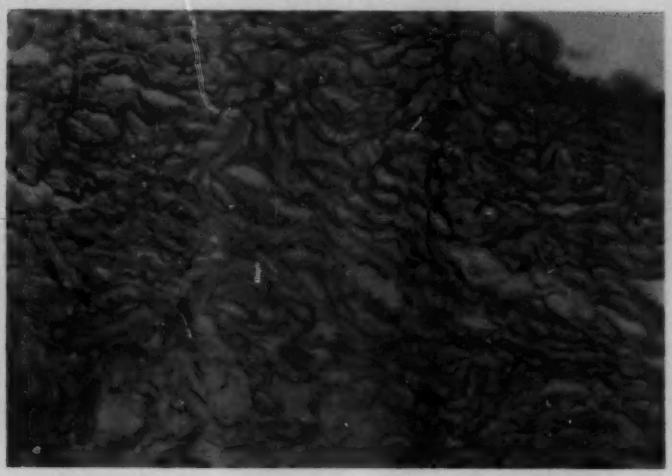

Fig. 3.—Reticular fiber development on the fifth day of healing of an incision made in a normal cornea. The reticular fibers are well developed at this stage.

fibroblasts, among which fibers could not readily be distinguished with hematoxylin and eosin stains. However, a rich network of reticular fibers could readily be demonstrated by the use of Wilder's silver stain (Fig. 3). Their orientation was completely irregular, except at the site of basement membrane formation. Wounds at this stage stained very lightly by the PAS technique. According to Glegg et al.,[3] this reaction indicates that smaller quantities of neutral mucopolysaccharides are attached to these fibers than to those of mature corneal connective tissue. These authors believe the PAS reaction is not with the ground substance but rather with carbohydrates attached to the fibers. In contrast, the metachromatic reaction of the new connective tissue was very striking and was far more intense than that of the normally metachromatic corneal stroma. The reduction in stromal metachromasia immediately adjacent to the cut, so apparent earlier, was still faintly discernible in some cases.

Radioautographs of healing wounds on the fifth and sixth days showed a very large amount of radioactive sulfate incorporated in the new and growing connective tissue. The area of marked sulfate deposition was sharply delineated from the rest of the cornea (Fig. 4), with its normal amount of sulfate incorporation. Accurate projection drawings of these radioautographs, when superimposed on similar drawings of hematoxylin-stained control sections, showed that the region of high sulfate activity was almost completely restricted to the new connective tissue, plus a narrow band of the neighboring stroma.

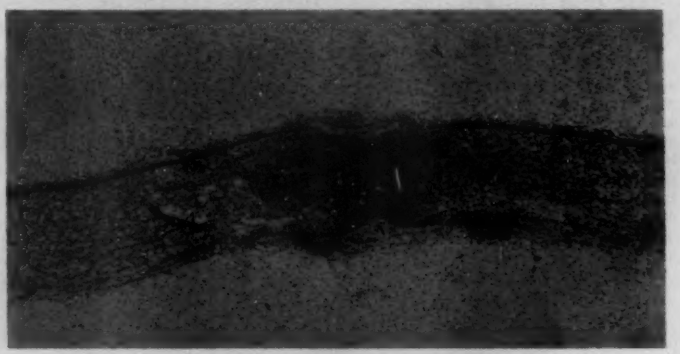

Fig. 4.—Radioautograph of a wound in a normal cornea on the fifth day of healing. Note the intense degree of sulfate incorporation in the precisely demarcated healing area.

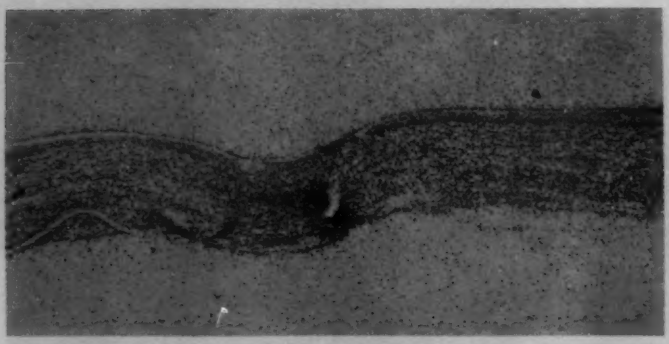

Fig. 5.—Radioautograph of a wound in a normal cornea on the 45th day of healing. Sulfate incorporation in the scar is still progressing at a higher rate than in the rest of the cornea.

This area is perhaps the same zone which on Day 1 was sulfate-free.

Healing at 7, 10, and 15 days had progressed steadily, without clearly discernible stages. Slight and decreasing infiltration of lymphocytes was observed. The disposition of the new connective tissue fibers changed from irregular to parallel bands arranged in a more nearly characteristic corneal fashion. Although this change began as early as the 7th day in many cases, a parallel arrangement was not found until the 15th postoperative day. The new connective tissue still gave a weaker PAS and a much stronger metachromatic reaction than did the normal corneal stroma. Radioautographs showed that sulfate incorporation was also very active, and it was sharply limited to the area of new connective tissue. Wounds of the 22-day stage appeared well healed, with the fibers arranged in a fairly parallel fashion, more cellular than normal and now stained more strongly with PAS, as if, in fact, they were of a nearly mature type. Metachromasia was reduced in intensity, and the radioautographs indicated that sulfate incorporation, although it was somewhat less than earlier, was still progressing at a rate greater than in normal corneal tissue. Two cases were studied at 35 and 45 days, and even at this late date both of them showed a slightly stronger metachromatic reaction and higher rate of sulfated mucopolysaccharide synthesis than normal corneal tissue (Fig. 5). These findings indicate that wound repair is still in progress.

Effect of Freezing on the Intact Cornea.

As a preliminary step to the study of the healing of incisions in corneas devitalized by freezing, the reaction of intact corneas to the freezing process was investigated. Sections from 24 eyes were examined after recovery periods ranging from 1 to 22 days. All cells in the frozen portion of the cornea had disappeared within 24 hours. At this time, there was already in progress an extensive invasion of polymorphonuclear leukocytes and fibroblasts, from the peripheral portions of the cornea. In most cases, it took place mainly in the posterior layers and large areas of the cornea were still cell-free. Lymphocytes first made their appearance on the second day. Freezing did not fundamentally affect the corneal staining reaction with PAS, but the stain was fainter in some cases which showed rather marked stromal swelling. This decrease was probably due to dispersion of the stainable elements rather than to a reduction in their total quantity.

The metachromatic staining reaction was only slightly less than normal at the 24-hour stage; however, from the second to the fourth day it was markedly reduced in the areas which had been frozen. Radioautographs of such corneas are extremely interesting, for they show only areas in which active incorporation of new sulfate is taking place and, unlike the metachromatic staining reaction, indicate nothing of what is already present. It was, therefore, very surprising to find unmistakable evidence of sulfate incorporation in the cell-

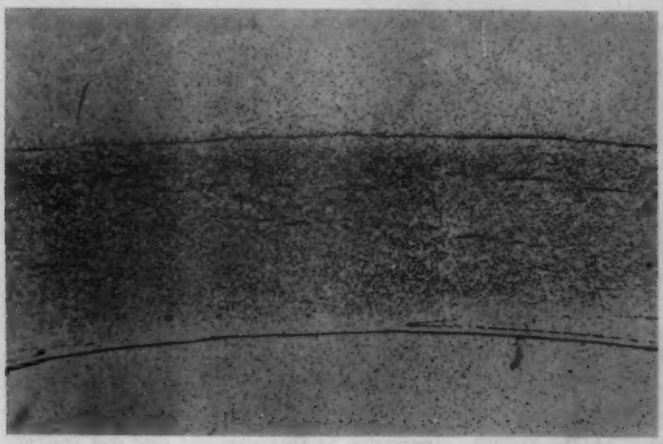

Fig. 6.—Radioautograph of an intact cornea 24 hours after freezing, showing that some S^{35}-labeled materials were incorporated in the corneal stroma from the 17th to the 24th hour after destruction of the cellular elements.

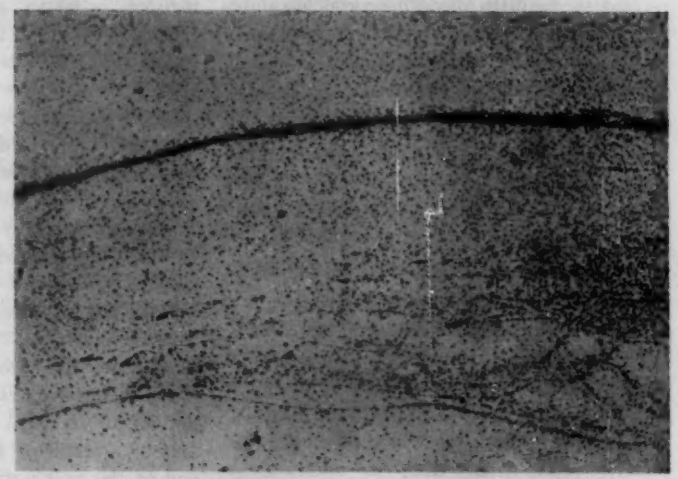

Fig. 7.—Radioautograph of a cornea on the second day after freezing, showing the junction of the devitalized zone (left), in which no sulfate has been incorporated, and the normal portion (lower right), in which sulfates are present.

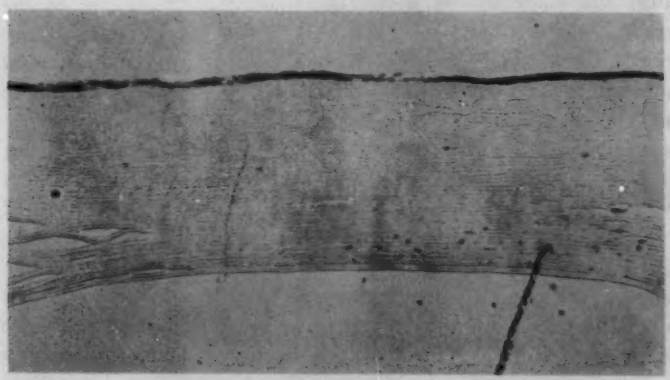

Fig. 8.—Photomicrograph of a section of the cornea shown in Figure 7. The junction of the devitalized, cell-free zone (left) and region of living cells (right) corresponds to the regions free from sulfate and of normal sulfate incorporation.

free zones of the cornea from the 17th to the 24th hour after freezing (Fig. 6). From the 41st to the 48th hour after freezing no sulfate was incorporated in the tissue, and, therefore, no sulfated mucopolysaccharides were synthesized during that period. Radioautographs of the central (previously frozen) cornea gave no greater reaction than did the background, where no tissue underlay the emulsion. The more peripheral corneal regions, whose cells had not been harmed, showed evidence of normal rate of sulfate incorporation. This is well illustrated in Figures 7 and 8, at the boundary of the normal cellular peripheral and central cell-free area. As the cornea became repopulated with cells during the second to the fifth day, there was no indication of resumption of sulfate incorporation in the tissue. The new cells consisted not only of polymorphonuclear leukocytes and lymphocytes but also of considerable numbers of fibroblasts and many dividing cells. Maumenee[2] has presented evidence showing that a few of these cells repopulating a devitalized central area of the cornea are derived from macrophages. Staining with toluidine blue showed metachromasia returning by the fifth day. Both the metachromasia and the returning cells were found predominantly in the posterior layers. By the sixth and seventh days the corneas were almost, although not completely, repopulated, and, in addition to fibroblasts, a few polymorphonuclear leukocytes, some lymphocytes, and many dividing cells were observed. At this time the metachromatic reaction was essentially normal and the radioautographs showed that sulfate incorporation had again resumed. Although the cornea had become completely cellular, the rate of sulfate uptake remained below normal through the 10th to 12th days.

By the 15th to the 22d day, the rate of sulfate incorporation and metachromatic staining of the cornea had returned to normal and probably also the cell population; however, without actual counts, this latter statement cannot be verified.

The Healing of Incisions in Devitalized Corneas.—The healing of wounds in corneas which had been frozen progressed much more slowly and with much greater variation than that of wounds in normal corneas. The epithelium, which had disappeared over wide areas as a result of freezing, did not recover the surface and close the incision until the second day. The inflammatory response was much greater, and the corneas were turbid over a considerable area. Stromal swelling also was more marked than in the control eyes. Inasmuch as this swelling was not restricted to the tissue immediately adjacent to the incision, a larger area of cornea was affected. Although the edema was usually reduced by the 7th day, it sometimes persisted through the 10th day. In two instances the corneas were swollen at the 15th and the 22d day, respectively. At 24 hours many polymorphonuclear leukocytes, as well as a few macrophages and lymphocytes, were already at the wound margin. In only one of four cases had fibroblasts reached the wound by this time. However, by the end of the second day two of the four wounds had fibroblasts at the edge of the incision, though no new connective tissue fibers had formed. The PAS reaction of the corneal stroma was pale, probably as a result of stromal swelling. At the end of the first postoperative day the metachromatic reaction was somewhat reduced and the zone immediately adjacent to the cut stained still more faintly, in a manner similar to that seen in wounds of normal corneas. By the second day, with more marked corneal swelling, metachromasia was almost absent. Inasmuch as a similar reaction was noted in unwounded corneas without much swelling, this absence of metachromasia need not be considered the result of dilution of the stainable material. In all cases, radioautographs indicated that the central corneal region had some sulfate incorporation at the 24-hour stage. In a

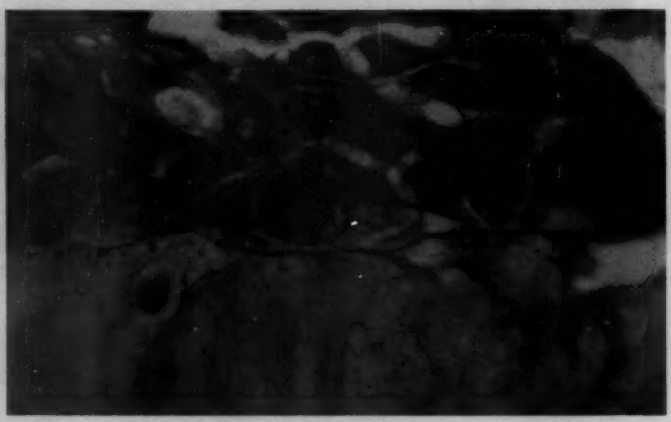

Fig. 9.—Earliest formation of reticular fibers in a wound made in a cornea devitalized by freezing. This section shows a wound in the fifth day of healing. Note the close association of reticular fibers with the epithelium.

few eyes it was much reduced immediately adjacent to the cut, and in no instance was there any indication of a concentration of sulfate at the margin of these recent wounds. By the second day the stromal sulfate synthesis was nil, and still no formation of sulfated materials at the wound edge could be demonstrated. The invasion of polymorphonuclear leukocytes had subsided, but some macrophages and lymphocytes were present by Day 5. In all cases the fibroblasts had succeeded in reaching the cut, although often the anterior corneal layers were still cell-free. A large number of mitotic figures was found in the stromal cells during this and the succeeding few days. It was obvious from study of the sections that cells do not reenter the devitalized area evenly, for considerable portions of corneal tissue remained without them for some time.

In only two of the five five-day specimens examined were traces of reticular fibers found (Fig. 9), and in one of these their identity was questionable. The extent of fibrillogenesis in these wounds was equivalent to that seen in the first and second days in normal corneal wounds, thus indicating a three- to four-day delay in the formation of the first connective tissue fibers. Metachromasia of the cornea was markedly reduced about the cut and in a wide area coincident with the previously frozen region. In one instance the wound contained strongly metachromatic

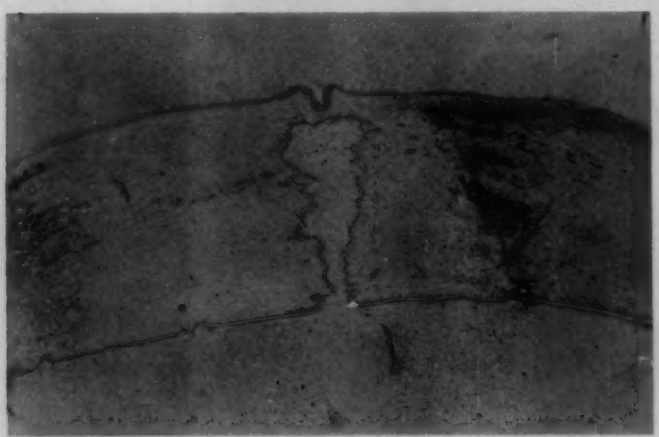

Fig. 10.—Radioautograph of wound in a devitalized cornea on the sixth day of healing. A narrow band of newly sulfated ground substance is seen at the edge of the cut. The stroma adjacent to the wound is essentially free from sulfated mucopolysaccharides. The ability to synthesize sulfated material is returning to the devitalized area unevenly.

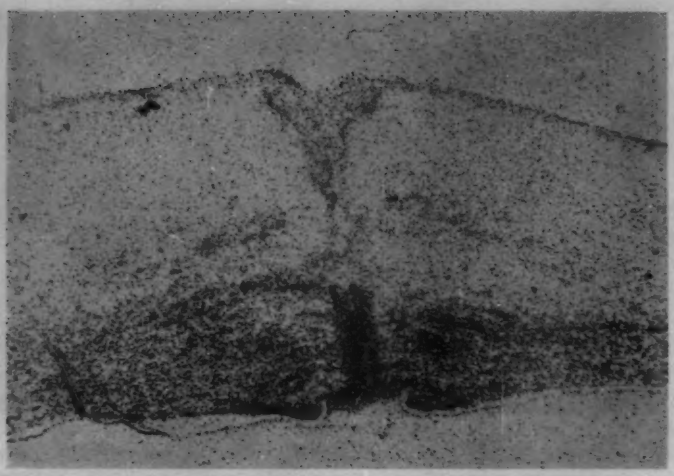

Fig. 11.—Radioautograph of five-day wound made in a devitalized cornea, showing uneven return of ability to synthesize sulfated corneal material. Note that sulfation has occurred in a cellular region (see Fig. 12) and that some healing has taken place in this area.

material presumed to be newly formed connective tissue.

Radioautographs made on the fifth day of healing showed that the incisions were surrounded by a corneal stroma entirely free of newly sulfated materials. However, in each instance some indication of new formation of this type of mucopolysaccharide could be detected at the edge of the healing wound. In most cases the area of sulfate incorporation was extremely narrow (Fig. 10). Sulfating activity apparently is greatest at the edge of the cut and decreases in amount peripherally. Thus, streaks or bands of active regions appear to radiate from the cut in lamellae paralleling those of the cornea (Figs. 11 and 12). On the sixth or seventh day half of the cases showed healing similar to that described in the five-day series but in others serious defects in this process had become obvious. The most striking difference between the healing in the normal and devitalized corneas was the failure in about 40% of the latter cases to form a firm union in the posterior one-half or two-thirds of the incisions. These defects were found in the later stages, beginning with the seventh day. The fibrin clot, which at first sealed the wound, had disappeared and had not

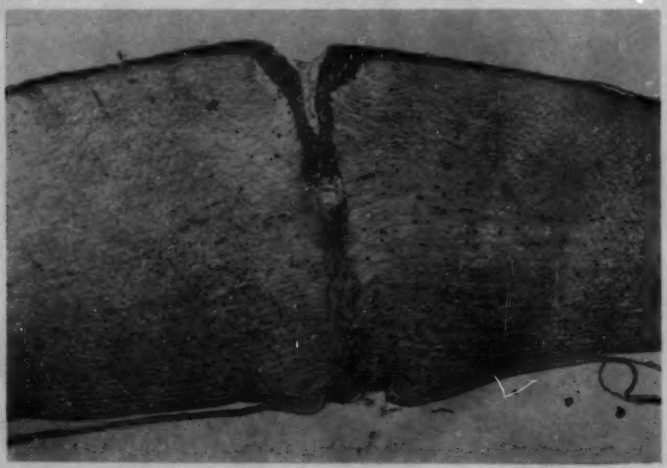

Fig. 12.—Photomicrograph of a section of the same cornea as that from which the autograph in Figure 11 was made.

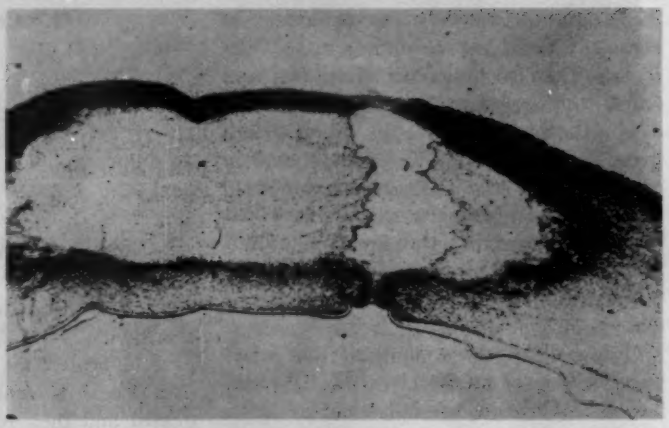

Fig. 13.—Radioautograph of 11-day-old wound made in a devitalized cornea. An intracorneal vesicle has formed, bordered by a thin corneal margin rich in sulfated ground substance. Except for this thin surface of sulfated material, the cornea is nearly devoid of ground substance. The entire wound area is in turn surrounded by an irregular corneal zone extremely rich in sulfated material.

been replaced with connective tissue. The wound, therefore, gaped posteriorly, creating an intracorneal cavity open to the anterior chamber (Figs. 13 and 14). In these cases, Descemet's endothelium grew into the cavity in an attempt to cover the posterior surface but succeeded only in partly lining the opening. Sometimes, very few fibroblasts were seen and they tended to line the cavity rather than to bridge it. The anterior margin of the incision, where healing first takes place in the normal cornea, was bridged by new connective tissue which formed a rather delicate union. Autolysis of the corneal substance did not create these defects, at least in the early stages, for the cut ends of the corneal lamellae appeared to be discrete, no evidence of phagocytosis was seen, and cellular infiltration in general was not excessive. Although very few new connective tissue fibers had been laid down, fibroblasts were present at the wound edge. One might assume that these difficulties occurred in eyes with very slow fibroblast migration. However, migration was generally completed within 48 hours, and the vesicle cavity formation was found first on the 7th and not commonly until the 10th day. Only in one case were there no fibroblasts at the cavity margin. Edema in even the 15- and 22-day cases was marked, but it is not clear whether this was a contributing cause or a result of extensive exposure of corneal stroma to aqueous humor. Although, in such cases, the metachromatic reaction was particularly uneven throughout the entire

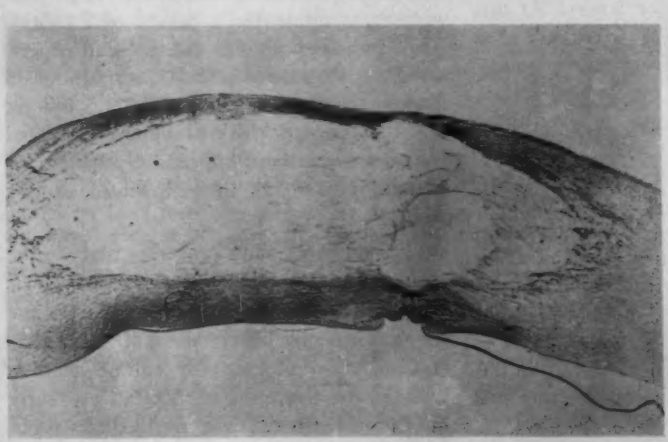

Fig. 14.—Photomicrograph of the corneal wound of which an autograph is shown in Figure 13.

cornea, it was always metachromatic in regions where new connective tissue was found. The distribution of sulfate was very diffuse and irregular. In a few cases seen 15 days after injury a reasonably well knit wound was obtained. Here the distribution of sulfate was less diffuse, being restricted to the area of new connective tissue. However, the amount of sulfate in these wounds was less than that observed in a similar wound made in the unfrozen contralateral eye.

Only half of the wounds of this series were well healed on the 11- to 17-day specimens. Infiltration of inflammatory cells, which had been so marked, was greatly reduced. The periodic acid-Schiff reaction of the newly formed connective tissues was the same as in the normal series, i. e., new lightly stained fibers contrasting with the strongly stained original corneal lamellae. However, in slides stained with toluidine blue, the stromal metachromasia was still reduced and, in one case, more so in the anterior than in the posterior layers. All new connective tissue was strongly metachromatic, as was seen in the normal series. At both the 22d and 45th days after injury wounds in the once devitalized corneas appeared to be well healed. The connective tissue fibers were parallel and gave a nearly normal PAS reaction. They were still somewhat more metachromatic than normal, with the most intense reaction being exhibited in the newly formed posterior layers. At this stage the original corneal stroma gave a completely normal metachromatic reaction.

From the 15th day on the stromal sulfate in the central corneal region appeared to be normal in amount, which suggests that the usual rate of function of the corneal corpuscles had returned. By the 22d day the new connective tissue was still synthesizing sulfated mucopolysaccharides at a rate greater than that of the normal stroma. However, the radioautographs did not indicate quite as great an activity in these eyes as in the wounds in normal corneas. Even by the 45th day the rate of sulfate uptake was still slightly elevated.

Comment

In recent years it has been generally accepted that even those tissues composed mainly of structural elements are regularly replaced, thus giving rise to a concept of "turnover rates" or "biological half-life" of tissue components. Studies have shown that approximately half of the chondroitin-sulfate content of skin is renewed every 7.7 to 10 days (Schiller[8] and Boström and Gardell[9]). Investigations with mucopolysaccharide molecules, labeled with S^{35} and C^{14}, have indicated the entire molecule rather than one of its components is completely degraded and then resynthesized. Therefore, when S^{35}-labeled sulfate is used as a marker of the sulfated mucopolysaccharides, one can be confident that he is investigating the metabolism of the entire molecule, rather than a process of de- and resulfation. Dohlman and Boström,[10] studying the metabolism of the sulfated mucopolysaccharides of the cornea, recorded no appreciable replacement of corneal sulfate in 17 or 18 days. This finding indicates a much lower turnover rate or lower half-life for the sulfated mucopolysaccharides of the cornea than of other tissues. These experiments were recently confirmed by Smelser, Copenhaver, and Quesenberry.[11] Using radioautographic methods, they showed that, while the sclera had a high rate of sulfated mucopolysaccharide metabolism similar to that of large arteries, the corneal sulfate was essentially stable for a period of 24 days. This greatly simplifies the present experiment, for the rate of sulfate incorporation in healing tissue may be compared to that in normal cornea, which maintains its sulfated constituents without appreciable change for periods as long as those involved in this study.

Undoubtedly, many processes precede the formation of sulfated mucopolysaccharides, but it was the earliest sign of new connective tissue elements observed in the wounds studied. Several cases of sulfate binding without the presence of fibers were seen, but in no instance was fibrillogenesis ob-

served without the presence of newly sulfated material. It would seem that sulfated mucopolysaccharides can be demonstrated by radioautography before metachromatic staining is observed. However, this may be due to the difficulty in seeing small quantities of metachromatic material arranged in a very thin line. Kodicek and Loewi,[12] investigating the regeneration of tendon, did not observe S^{35} before the seventh day. This may have been because the counting technique is less sensitive than the radiographic method. Upton et al.,[13] in their studies on the regeneration of muscle wounds, reported that sulfate was incorporated in wounds on the fourth day when fibrillogenesis was active.

Recently Dohlman [14] has investigated the incorporation of S^{35} in corneal transplants, using contact radioautographic methods. He noted considerable uptake of S^{35} in the wound edges between 8 and 25 days after keratoplasty. Radioactive sulfate incorporation was greater when large amounts of granulation tissue were present.

It is important to emphasize that fixation of sulfate requires the action of "prepared" cells, for it was observed in areas of fibroblast concentrations and was absent in the narrow cell-free zone sometimes found adjacent to new cuts. It was originally thought that a wound made in a devitalized cornea would heal at nearly the normal rate, because fibroblasts migrated so quickly from the periphery to the injured area. However, it is clear from the present studies that cells which are moving or have recently moved are not effective in the production of sulfated material. Apparently, the physiological mechanisms necessary for their rapid mobilization are not those involved in the synthesis of sulfated mucopolysaccharides. Therefore, the fact that cells are present or can migrate quickly to a wound does not preclude delayed wound healing. The time required for the physiological reorganization of these recent migrants explains in part the delay in healing observed in the present study. The variable route by which cells migrate from normal tissues through a devitalized area to a wound and the dependence of ground substance synthesis on these cells account for the extreme irregularity in the distribution of new sulfated materials seen in these wounds. This, in turn, is thought to explain not only the delay in healing but also the occasional bizarre healing patterns.

It is interesting to note that the ability to form sulfated mucopolysaccharides in a wounded and devitalized cornea is not slowly regained from the periphery but appears to "jump" to the cut, where it is restored first (Figs. 10 and 13), as if the injured area had a priority over the intact cornea.

The occurrence of some sulfate binding in the cornea 17 to 24 hours after freezing is difficult to explain. Boström and Mansson [5] found that dead tissue in vitro did not form chondroitin sulfate. Although the freezing technique used in these experiments destroyed the corneal cells, it apparently did not harm certain enzymes which were still able to fix the sulfate to some organic constituents. After 24 hours these enzymes or the organic constituents, or both, diffused out of the cornea and the incorporation of sulfate ceased.

The distribution of radioactive sulfate in the healing wounds correlated well with the metachromatic staining with toluidine blue. The absence of both reactions in the acellular area around the wound, their decrease after freezing, and the strong reactions in newly formed connective tissues were in agreement. It should be emphasized that the toluidine blue metachromasia indicates the quantity of mucopolysaccharides present, whereas the radioautographs indicate only the amounts of these materials which have been formed during the seven hours preceding the autopsy, i. e., the rate of formation. It is well established that toluidine blue metachromasia may be obtained not only with sulfated but also with nonsulfated mucopolysaccharides, such as hyaluronic acid. Our data revealed no case in which the metachromatic staining demonstrated the presence of this type of material when the

autographs did not indicate the presence of sulfate. In contrast to the metachromatic reaction, no correlation between S^{35} concentration and material stained with PAS could be made. The two reactions were not the same in the corneal stroma during the postfreezing period or in new stromal connective tissue.

Apparently reticular fiber formation begins earlier and proceeds faster in the cornea than in the abdominal wounds studied by Dunphy and Udupa,[15] who found them first at four days and maximally developed on the seventh and eighth days. In the present study the first fibers to form were fine and argyrophilic and were seen in contact with the epithelium. It is tempting to think that there is some significance in the close relationship of the glycogen-rich epithelium and the adjacent concentration of fibroblasts. Perhaps this area is one of high oxygen tension and of richer nutrition obtained from the glycogen. Healing, which is regularly observed in the anterior portions of these incisions, starts with these first reticular fibers. Perhaps this anteroposterior healing pattern is an expression of a simple nutrition and oxygen gradient. In vascular tissue this gradient begins at vessels, but in the avascular cornea the atmosphere and nutrition-rich epithelium replace this function of the vessels.

The formation of fine reticular and young collagen fibers in a rich ground substance was not surprising, but after mature fibers had developed it was evident the rate of mucopolysaccharide synthesis continued at a much higher level than in normal cornea. During this reconstruction period the irregularly arranged fibers are removed and replaced by parallel lamellae. Perhaps one can postulate that the ground substance is also reorganized and, therefore, that the turnover rate of sulfated materials is greater in a healing wound than in the normal cornea.

Summary

The normal cell constituents of connective tissue adjacent to an injury are most important in the healing process. There is a delay before other cells which migrate to the site of injury can begin their work of forming ground substance of fibers.

If a cell population is destroyed by freezing, the ground substance is not replaced at a normal rate for a considerable period after the cells have been restored. In addition, it is possible that inflammatory cells break down the existing ground substance at a rate greater than normal and thereby produce a considerable deficit in temporarily devitalized tissues.

Ground substance is the earliest new connective tissue element found in a healing wound. The formation of reticular fibers occurs almost simultaneously and may occur in wounds such as those described here as early as the 17th to 24th hours.

The process of wound healing in a temporarily devitalized cornea may be delayed from three to four days, and in a high percentage of cases the subsequent healing process is extremely imperfect.

Miss Caroline White gave technical assistance.

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Case Reports

Toxicity Due to Acetazolamide (Diamox)

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The increasing use of acetazolamide (Diamox) by ophthalmologists in the therapy of open-angle, angle-closure, and the secondary glaucomas must inevitably result in an increasing number of toxic side-reactions. It is our feeling that the occurrence of leukopenia in combination with exfoliative dermatitis in a patient is of sufficient interest to warrant report and should alert ophthalmologists to the possibility of these side-reactions.

Report of Case

A 56-year-old white male executive has been under our care since August, 1955, for open-angle glaucoma. He had had an Elliot trephination in O. D. in London in 1952 and an iridectomy in O. S. in 1953. He had been using 2% pilocarpine t. i. d. in O. S.

Our examination revealed the following: Vision was correctable to 20/40 O. D. and 20/30 O. S. Lids were normal; conjunctiva and cornea were clear O. U. There was a functioning trephine in O. D. and a wide iridectomy in O. S. Motility was normal and media were clear O. U. Examination of the fundi revealed glaucomatous cupping and pallor, more advanced in the right disc. Determination of peripheral visual fields revealed some nasal loss O. D. Central fields showed enlargement of each blind spot and early Bjerrum scotoma in the right nasal superior field. Gonioscopy revealed open angles in each eye. Tension was O. D. 20 mm. Hg and O. S. 27 mm. Hg (Schiøtz). The patient was advised to continue pilocarpine t. i. d. in O. S.

His condition remained stable until December, 1955, when the tension rose to 40 mm. in O. S. This was controlled with difficulty with 0.25% physostigmine (eserine) q. i. d. In May, 1956, the use of physostigmine had to be discontinued because of conjunctival irritation, and 3% pilocarpine six times a day was substituted. The pressure in O. D. remained at a normal level throughout this time. In November, 1956, the tension in O. S. rose again and remained at a level of approximately 35 mm. At this time progressive field loss was noted in O. D. and progressive enlargement of the blind spot, in O. S. The field loss in O. D. in the face of a normal tension was felt to indicate progression of glaucomatous nerve atrophy. The changes in O. S. we believed to be on the basis of increased tension. In January acetazolamide therapy, 125 mg. t. i. d., was begun in addition to continued miotic therapy, and the pressure was brought within a normal range.

On May 31, 1957, the patient developed exfoliative dermatitis of the skin on the palmar surface and between the fingers of both hands. Acetazolamide was discontinued immediately, and he was sent to the laboratory for a complete blood cell count. Examination revealed RBC 4,500,000; hemoglobin 15 gm.; WBC 3050, with 60% polymorphonuclear cells, 21% lymphocytes, 9% monocytes, 4% eosinophils, and 1% basophils. The patient was taking no other systemic medication, and we assumed that both the white blood cell depression and the exfoliative dermatitis were due to acetazolamide.

No specific therapy was instituted. The exfoliation of skin cleared spontaneously within several days. After one week a repeat complete blood cell count revealed

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hemoglobin 14.6 gm.; white blood cell count 7950, with 68% polymorphonuclear cells, 26% lymphocytes, 4% monocytes, and 2% eosinophils. Tension continued to be poorly controlled with 3% pilocarpine six times a day.

Comment

Acetazolamide, being a sulfonamide derivative, naturally shares the toxic reactions observed with the use of any sulfonamide. Thus Schwimmer, Schaffer, and Guido [1] reported a febrile reaction, similar to that which sometimes accompanies sulfonamide therapy, and Breinin and Gortz [2] reported a typical sulfonamide rash in two patients receiving acetazolamide. The rash in each case subsided spontaneously after cessation of therapy. The latter authors suggested that the full spectrum of sulfonamide toxicity might eventually become evident with wide acceptance of this drug.

Pearson, Binder, and Neber [3] reported agranulocytosis due to acetazolamide. More recently, Underwood [4] reported a fatality due to bone marrow depression as a result of acetazolamide therapy. Our patient exhibited both skin and hematopoietic toxicity.

When acetazolamide is prescribed for long-term therapy, the physician must remain aware of the possible toxic nature of the drug. The patient should be cautioned to report any unusual skin rash, and periodic blood cell counts should be ordered. A precipitous drop in formed blood elements or toxic skin manifestations should call for immediate cessation of therapy.

Summary

A case of leukopenia and exfoliative dermatitis due to acetazolamide (Diamox) is reported.

Periodic complete blood cell counts and careful observation for toxic skin manifestations are advised for all patients receiving prolonged acetazolamide therapy.

525 Park Ave. (21).

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Intraocular Foreign Body

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The presence of an intraocular foreign body greatly enhances the likelihood of complications, altering the prognosis and the therapeutic approach to the problem of perforating ocular injuries. X-ray studies are usually valuable in determining the presence and location of a foreign body but occasionally can be misleading. In the following case x-rays failed to reveal the presence of a relatively large foreign body which was discovered at the time of evisceration of a globe, three weeks after a perforating injury.

Report of Case

A 7-year-old white boy was admitted to the Manhattan Eye, Ear and Throat Hospital on March 2, 1955. One hour prior to admission, while playing he had been struck in the left eye by a pencil. Examination revealed a 5 mm. horizontal penetrating laceration of the left cornea, with laceration and prolapse of portions of iris and lens. Visual acuity was reduced to counting fingers at 12 in. The fundus could not be visualized, owing to the changes in cornea and lens. Examination of the right eye was completely normal. Routine x-ray studies revealed no evidence of a radiopaque foreign body (Figs. 1A and 1B).

The patient was prepared for surgery. With use of general anesthesia, the prolapsed and incarcerated tissues were excised; the anterior chamber was thoroughly irrigated to remove as much of the cortex and uveal fragments as possible, and the corneal laceration was closed with four interrupted 000000 black nonabsorbable surgical (silk) sutures; 1500 units of tetanus antitoxin was administered, and administration of a preparation of peni-

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Fig. 1A (Case).—Anteroposterior x-ray of orbit, showing failure to reveal the presence of a radiopaque foreign body.

Figure 1B

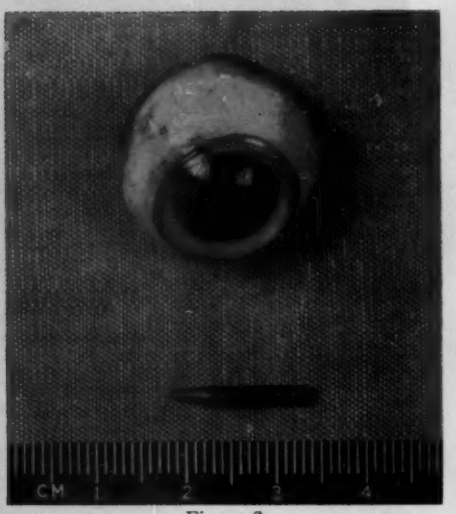


Figure 2

Fig. 2.—Pencil "lead" 15 mm. in length. Cat's eye for comparative size.

Fig. 1B (Case).—Lateral x-ray of orbit, showing failure to reveal the presence of a radiopaque foreign body.

cillin and dihydrostreptomycin (Combiotic), 2 cc. i. m. twice a day, was begun.

On the second postoperative day the patient had "spiked" fever (temperature to 103.2 F). The lids and conjunctiva were edematous and congested, and the anterior chamber was filled with thick yellow purulent exudate. Cultures were taken, and therapy with chloramphenicol (Chloromycetin) was instituted both by local (0.5% solution every hour) and systemic (500 mg. first dose and 250 mg. every four hours) routes. In addition, 10,000,000 units of typhoid vaccine was given intravenously. The cultures revealed hemolytic Staphylococcus pyogenes var. albus sensitive in vitro to all antibiotics tested.

There was good initial response to therapy, with absorption of hypopyon and diminution of all inflammatory signs. After two weeks, however, an apparent "escape" from therapeutic control occurred, with recrudescence of endophthalmitis. Despite all treatment, softening of the globe and loss of light perception ensued. On March 24, 1955, with use of general anesthesia, an evisceration was performed, with implantation of a 14 mm. plastic sphere into the scleral shell. During the procedure a piece of pencil lead 15 mm. long was unexpectedly discovered and removed from the globe (Fig. 2). The postoperative course was benign, and the patient was discharged with a temporary prosthesis and good cosmetic result on April 6, 1955.

Comment

A large foreign body with a solid metallic appearance would be expected to be easily demonstrated by x-ray. The misnomer pencil "lead" further serves to confuse. Pencil "lead" is of course in reality graphite, a soft native carbon with metallic sheen. The comparative radiotransparency of carbon (0.480) approximates that of bone (0.560) when compared with iron (0.101) or lead (0.055).[1] Therefore, the presence of intraocular carbon foreign bodies can only be demonstrated by the bone-free technique of Vogt[2] or Lind-

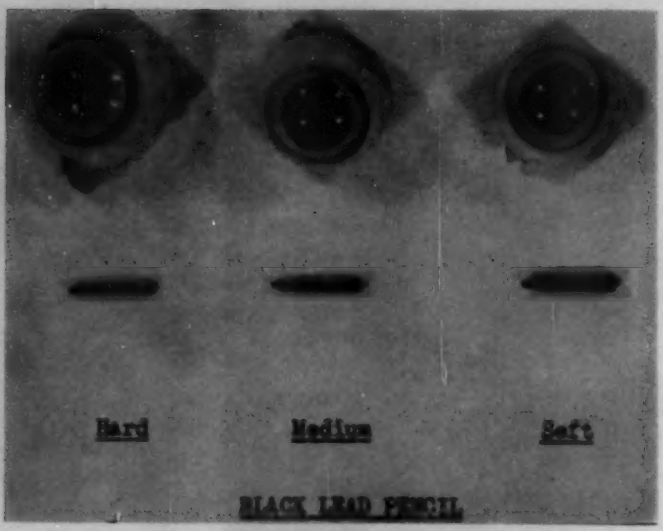


Fig. 3.—Fifteen millimeter lengths of pencil "lead" before insertion into enucleated cats' eyes.

blom.[3] In this process dental x-ray films are used and placed in such a position with reference to the orbit and globe that background bone is eliminated from the picture. The following study serves to demonstrate this clearly.

Lengths of graphite 15 mm. from hard, medium, and soft lead pencils were inserted into enucleated cat eyes through a small posterior stab incision (Fig. 3). Routine anteroposterior and lateral x-rays taken with the eyes placed in the orbit of a skull failed to reveal the presence of the foreign bodies (Figs. 4A, 4B, and 4C). However, the foreign bodies were readily demonstrated by a bone-free technique Fig. 5).

The presence of intraocular carbon foreign bodies appear to be an uncommon occurrence. Duke-Elder cites six reported

Fig. 4A.—Anteroposterior and lateral x-rays of skull with cat's eye containing foreign body inserted in the orbit. No evidence of the foreign body can be seen.

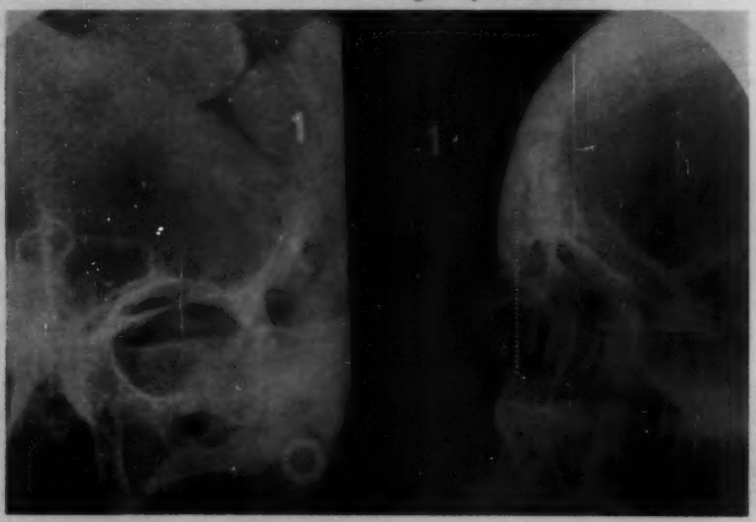


Fig. 4B.—Anteroposterior and lateral x-rays of skull with cat's eye containing foreign body inserted in the orbit. No evidence of the foreign body can be seen.

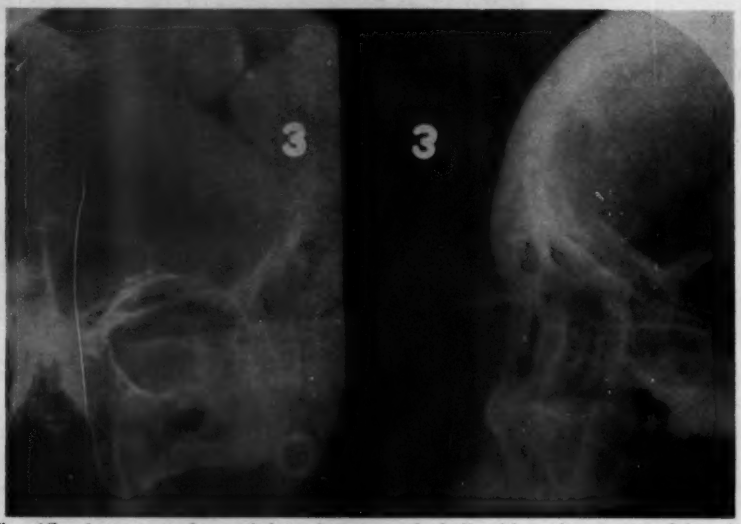
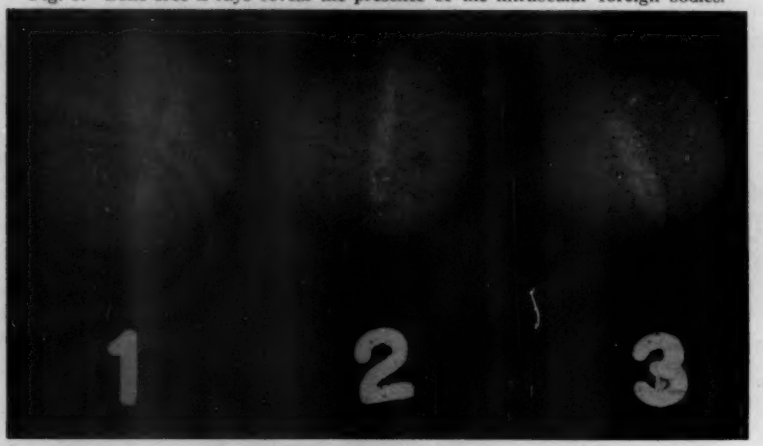


Fig. 4C.—Anteroposterior and lateral x-rays of skull with cat's eye containing foreign body inserted in the orbit. No evidence of the foreign body can be seen.

Fig. 5.—Bone-free x-rays reveal the presence of the intraocular foreign bodies.



cases,[4,9] and a review of the literature fails to disclose any others.

Summary

A case of intraocular carbon foreign body is reported in which routine x-rays failed to reveal its presence. X-rays by bone-free technique are therefore suggested for any case of suspected intraocular foreign body where routine studies are negative.

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Clinical Notes, New Instruments and Techniques

A Precision Light Source for Electroretinography

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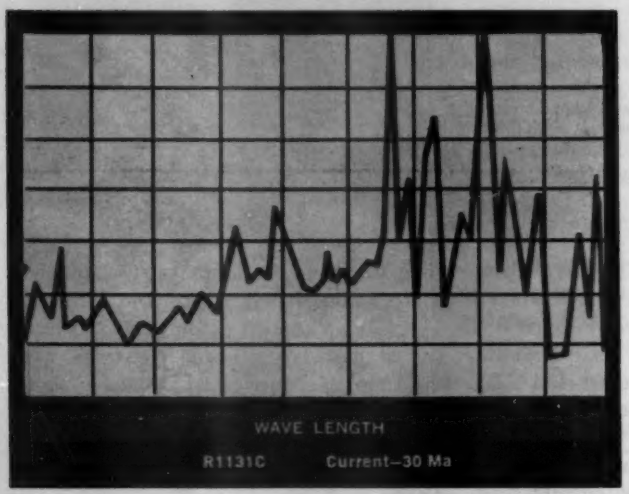

Fig. 1.—Spectral composition of light from tube.

The stroboscopic light source customarily used for clinical electroretinography has several disadvantages when used for precise laboratory work. The most serious of these are the variance in intensity with speed of flash, the variance in site of flash in the gas-filled tube, and the inability to control the duration of flash.

It is also impossible to accurately coordinate two or more stroboscope units to flash alternately, which is of importance in work recently undertaken.

With these factors in mind, a new light has been devised.

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From the Division of Electrophysiology, Department of Research, New York Eye and Ear Infirmary.

Supported by grants from The Fight for Sight Fund of The National Council to Combat Blindness, The National Society for the Prevention of Blindness, and The Snyder Foundation.

The source of light is a "glow modulator" tube, type R 1131-C, which furnishes a source of light 0.093 in. in diameter and has an instantaneous on and off characteristic, whose intensity can be adjusted through a large range and which can be powered from any one of a number of laboratory stimulators.

It requires a potential of 225 volts to start the light and it can be driven over its

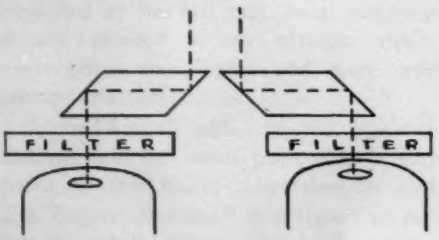

Fig. 2.—Diagram of method of using prisms to approximate beams from two tubes.

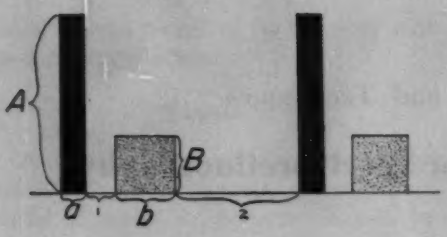

Figure 3

Fig. 3.—Scheme of variable parameters of stimulation available with use of two tubes. Intensity (*A* and *B*) of each monochromatic light, duration (*a* and *b*) of each, and time between stimuli (*1*) and between cycles of stimuli (*2*) can each be varied independently.

Figure 4

Fig. 4.—Photograph of flash unit.

maximum rated load, at 250 volts, without damage, for short periods. A small amount of ambient light is required to start the tube. If the unit is used in total darkness, a strip of radium-impregnated foil may be used to maintain ionization. The spectral characteristics of the light, which is white to the eye, are shown in Figure 1.

By utilizing proper delay circuits it is possible to flash two or three or more of these lamps alternately. This has been found to be of great value in alternate stimulation with different monochromatic lights. By utilizing parallelepiped prisms it is possible to bring the lights of two of these sources immediately adjacent to each other (Fig. 2). Variation of duration and intensity of flash is continuously variable when the lamp is connected to a suitable source of power.

Figure 3 shows schematically the types of variation of stimulation possible with the device.

Summary

A new source of light for electroretinography is described.

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Annual Reviews

Strabismus

Review of the Literature for 1957

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Circumstantial evidence is available to anyone who wishes to theorize that an increase in incidence of strabismus is a penalty attributed to "progress" of our civilization, since it is four times commoner among the white Australians than among the aborigines of New Guinea.[1]

Basic Science Literature

Sensory.—Fusion reflexes are conditioned psychic responses which imply extensive cortical associations.[2] The sensory component of fusion is complicated by the fact that the sharp macular images have to be almost exactly superimposed while the blurred peripheral images can be fused with less accurate superimposition.[3] Peripheral fusion is present often in the absence of macular fusion, and this may be sufficient to maintain an amblyopic eye in proper position. However, good depth perception is dependent upon high-quality macular fusion, which is only possible with good central vision in each eye plus precise alignment of the foveas. Physiological diplopia is simultaneous perception by right and left occipital cortex of the same object imaged binasally or bitemporally. Stereoscope vision is not disturbed by it. Patients with homonymous hemianopia appreciate depth with the intact part of their visual field; yet they do not appreciate physiological diplopia. Patients with heteronymous hemianopia do not have binocular depth perception but possess physiological diplopia.

Monocular diplopia is proven to be impossible in the presence of normal binocular vision by analyzing the perceptions obtained from a clever dissimilar target presented in a haploscope.[4] The study cited points out how a German psychologist misinterpreted experimental facts that led to the incorrect conclusion that monocular diplopia was possible under normal circumstances.

Bitemporal disparity gives rise not only to a convergence impulse but also to the perception of nearness. This is demonstrated by projecting equal-size ring targets so arranged that various degrees of bitemporal disparity must be fused. The rings producing the greatest bitemporal disparity appear smallest and nearest.[5] A monocularly viewed ring placed among the others viewed binocularly will assume an apparent size and location that is midway between that perception produced by the most and least bitemporal disparate rings. This indicates that objects viewed monocularly within our visual fields are conditioned in apparent size and location in depth in accord with binocularly viewed objects. Objects seen monocularly but projected onto either the higher retinal positions or the more temporal positions appear smaller and nearer than those projected onto the lower or nasal retinal positions. This is explained by the fact that lower and more nasally situated objects oftener require convergence than higher and more temporally situated objects.

A modification added to the Howard-Dolman test for depth perception is supposed to test height perception as well. The Zagora Rod test[6] is designed to permit the top half (movable) of the rod to be laterally aligned with the lower half

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(stationary) of the rod (depth perception) and also to be vertically adjusted so that the two halves appear as one continuous rod (height perception). The errors in lateral and vertical adjustment of the top half (movable) of the rod can be read off from millimeter scales.

A study of correlating the measurement of depth acuity determined on the Howard-Dolman two-rod apparatus with stereopsis suggests that stereopsis is not the principal basis of depth perception.[7] More important to depth perception is the vernier acuity.

The quantity of heterophoria qualitatively diminishes stereoscopic acuity.[8,9] Statistically, at least, this is so, but, on the other hand, 13 of 1536 youths between 17 and 22 years of age with orthophoria and supernormal visual acuity either had total lack of stereopsis or misunderstood the test.[9] Since heterophoria is associated with poorer stereopsis, heterophoria is suggested to be a cause of accidents among metal workers[8] and poor close-formation-flying performance among fighter pilots.[9]

Hypoxia corresponding to simulated altitudes of 19,000 to 25,000 ft. produces a significant decrease in stereoscopic acuity.[10] Hyperoxia (supplementary oxygen at atmospheric pressure) normalizes stereotest values in subjects with poor stereoscopic acuity.[10]

A phoria at sea level may become a tropia under hypoxic high-altitude conditions owing to induced changes in eye-muscle balance. Consequently, a phoria should be investigated while the pilot applicant is in a low-pressure chamber at a simulated high altitude to determine whether diplopia replaces binocular vision.[9]

Verhoeff reaffirms his opinion that reducing the luminosity of the image presented to one eye diminishes the stereoscopic effect.[11] His original interpretation on this matter, drawn from experimental observations, was published in 1933,[12] but Ogle and Groch[13] reached the opposite conclusion from their studies published in 1956.

Motor.—Reporting low-voltage electromyographic findings in extraocular and levator muscle paralysis is commonplace now.[14] However, 1957 was the year that Breinin managed to have recorded in medical literature a host of new ideas, plus confirmation in some cases and denial in others of old ideas, postulated in the days when the electrical charge which spreads over a contracting bundle of muscle fibers had not been tamed as a tool.

When the surgical plane of anesthesia is reached, all firing ceases; in deep sleep there are intervals of complete electrical silence for as much as a minute or two at a time.[15,16] This implies that the true anatomical position of rest, determined only by anatomical factors of orbital osteology, extraocular muscles, and their attachments to the globes and surrounding fascia, is encountered during anesthesia. This position is usually divergent.

The vertical recti are not accessory adductors, nor do the obliques contract to assist in abduction.[16,17] These cyclovertical muscles maintain a constant level of discharge in straight level right and left gaze, the elevators balancing the depressors. According to Breinin, "Whatever component of abduction or adduction may be manifested by the obliques and recti will be a consequence of the relation of the muscle plane to the center of rotation of the globe." Both elevators fire on upward gaze and diminish activity on downward gaze, regardless of whether the eye is adducted or abducted; the depressors follow the inverse pattern. However, the vertical recti may be somewhat more active in executing a vertical movement in abduction while the oblique muscle firing is preponderent in the position of adduction. The discharge of cyclovertical muscles upon head tilt has not been reported yet.

Verhoeff (1947)[18] had suggested that the cocontraction of the vertical recti enabled the maximally converged eye to adduct

further when a conjugated adduction movement was added. Electromyography does not bear out contraction of the vertical recti under this circumstance, but there is elicited an increment in the already heavily firing medial rectus when the conjugate adduction movement is added.[16,17]

Upon exceeding the near point of convergence, while maintaining fixation on a slowly approaching target, the eye that gives up fixation will deviate laterally and the tracing shows increase in lateral rectus firing and decrease in medial rectus firing.[19] The lateral and medial rectus muscles of the fixating eye show no change. This holds regardless of whether the convergence be symmetric (target approaching on midline course) or asymmetric (target approaching on course toward one eye). There are no reported electromyographic findings for rapid changes in asymmetric convergence induced by suddenly changing fixation from far to near. It is reasoned, however, that such electromyographic findings would bear out the electro-oculogram (Alpern and Wolter, 1956)[20] and photographic (Westheimer and Mitchell, 1956)[21] analysis of a rapid saccadic version movement followed by a slow convergence movement. Accommodative convergence studies performed by introducing minus lenses before the unoccluded eye and vergence studies investigated by using either prisms or haploscope produce the expected electromyographic changes in firing of the horizontal recti.[19]

Electromyography records the effects of drugs on the contraction of the extraocular muscles. Though succinylcholine chloride paralyzes skeletal muscles and consequently is used in anesthesia for its curare-like effect, it causes a brief and marked contraction of the extraocular muscles, sufficient to raise the intraocular pressure and make its use contraindicated for intraocular surgery.[16,22] Edrophonium chloride (Tensilon) reverses the fatigue phenomenon recorded electrographically in myasthenia gravis. The fatigue phenomenon is manifested in a muscle required to make a sustained effort by the characteristic progressive fall-out of firing units until there is practically no firing at all.[16,17,23]

One of the chief benefits of electromyography is harvested in the field of ophthalmoneurologic diagnosis.[16,24,25] Usually the paretic muscle retains a surprising amount of electrical activity; the irregularity and sparseness of recruitment, the amplitude of potential, and how well sustained the firings are reflect the degree of paresis. Also, there is diminishment of the "interference" pattern, e. g., single unit discharges in its field of action. A totally paralyzed muscle may show complete electrical silence, but, other than in diabetic neuropathy of the third nerve, the silence does not last longer than two weeks.[25] By this time, either denervation or recovery is usually manifest. Denervation is identified by fibrillations which are recorded as isolated low-potential pick-ups of spontaneous single muscle fiber contractions unrelated to volition. This finding makes the chances of recovery hopeless.[16,24,25] A recovering palsied muscle begins to record rhythmic discharges of coupled or duplex units similar to those which occur in sleep. These are called polyphasic waves and represent purposeless temporal or spatial dispersion of nerve action current. It is postulated that in diabetic neuropathy there is a focal lesion in the nerve trunk or nucleus and that the nerve block is produced by compression.[25] Subsidence of this lesion, which may require more than two weeks, permits resumption of activity.

Pseudoparesis is suspected if a forced duction test does not permit movement into the field of action of the "palsied" muscle. This is frequently encountered in esotropia, in which case the lateral rectus has been assumed to be palsied. Also, in the superior oblique tendon sheath syndrome the ipsilateral inferior oblique is often considered to be paralyzed. However, electromyography can be absolute in denying the primary pathology to be paralysis of the

lateral rectus[16,24] or of the inferior oblique.[25]

Hypercontraction of the medial recti has been revealed to cause spastic esotropia, thus ruling out bilateral weakness of the lateral recti as a cause.[24]

Either a fibrotic lateral rectus or abnormal attachments to the medial rectus have been previously described as causes of Duane's retraction syndrome. Electromyography has opened the door to a third cause.[16,24] Some central disturbance had had the result that the weak lateral rectus contracted only when the medial rectus fired, thus producing enophthalmos. The stretch reflex was proven not to be the cause of the lateral rectus contraction, since the lateral rectus did not fire when the globe was passively adducted.

Aberrant third nerve regeneration has been previously described as permitting a normal abduction movement, whereas all other attempted movements result in adduction, lid retraction, and miosis.[16,24,25] This has been explained previously and confirmed by electromyography to be due to inhibition of third nerve innervation on abduction. All other movements require third nerve innervation, and this results in elevators and depressors neutralizing one another while the medial rectus, levator, and sphincter pupillae act unopposed.

Progressive nuclear ophthalmoplegia behaves electromyographically as a muscle dystrophy, since firing of muscle units is intact, with retention of interference pattern, but the amplitude of each unit firing is low, owing to loss of a certain percentage of the individual muscle fibers which collectively comprise the normal firing units.[16,24,25] A relationship and consequent difficult differentiation between myasthenia gravis and external progressive ophthalmoplegia has been postulated.[26] However, despite the slight improvement a dystrophic patient may exhibit in amplitude of motor unit firing potentials with edrophonium injection, differentiation by electromyography between the two disorders is possible.[16,24,25] Without use of an anticholinesterase drug, myasthenia is characterized by a fall-out of unit firing but what firing there is takes place at full potential. Dystrophy is identified by sustained firing of the units but with a potential of low amplitude. With edrophonium the myasthenic full-potential unit firing increases in rapidity (fall-in) while the dystrophic firing potential may be augmented.

Dysthyroid ophthalmoplegia in the early stages reveals normal firing of the palsied muscle.[25] The assumption is that the turgescence of the orbital tissues mechanically interferes with motility. Later in the disease, pressure or toxic factors may give tracings typical of either nerve damage or muscle fiber loss.

Nystagmus is a neurological disorder that lends itself well to the critical study of electromyography.[16,24,25] By no better method can the reciprocity patterns of antagonists be investigated.

The motor side of a tension reflex within the extraocular muscles has been elucidated by electromyography.[16,27] The sensory portion of this reflex was established by Cooper, Daniel, and Whitteridge (1955), describing the muscle spindle stretch receptors and recording the stretch discharges in third, fourth, and sixth nerves, via the fifth nerve and in the brain stem.[28] Electromyography records a baseline recruitment in the normal muscle while the eye is in the primary position. Severing the muscle from the globe and allowing it to retract back into the orbit causes all firing to cease.[27] The severed muscle fires upon volition to look into its field of action. Stretching the cut muscle restores firing in the primary position, but no amount of extra stretching augments the firing above the primary position baseline of the normal muscle. Furthermore, the reciprocity mechanism that provides graded contraction and relaxation of antagonist as the eye is moved away from the primary position is lacking after the muscles have been severed from the globe and retracted into the orbits.

The agonist abruptly fires, while the antagonist is electrically quiet. Another approach used to build up the case for the stretch reflex is accomplished by considering those instances of anomalous innervation that occur in some recovering paretic muscles to be sensitized stretch reflexes. For example, a recovering paretic lateral rectus may contract more when the eye is either volitionally or passively adducted than when abduction is attempted.

More evidence has been acquired which points toward the slow smooth vergence movements being of the order of autonomic innervating system actions while the fast jerky version (saccadic) movements are accomplished by the somatic nervous system. In last year's review [29] I commented on the facts that a saccadic movement is carried out at about 400 degrees per second, while the vergence is achieved in the range of 8 degrees per second, and that separate histological types of motor endplates in the extraocular muscles trigger off each of these movements.[20] Also, in sudden asymmetric convergence in changing gaze from far to near there is first a saccadic movement which aligns the eyes so that the near fixation point bisects the ultimate convergence angle. This is followed by the slow convergence until the visual axes intersect at the near fixation point.[21] This same observation has been repeated and confirmed, but it was further noted that if the left eye was occluded while the right changed fixation from far to near, both targets being on the fixation axis of the right eye, all movements were damped in the right eye while the left made a smooth slow adduction movement.[30] This was explained by there being no reason to make a saccadic movement if only one eye is fixating; however, binocular vision requires a bifixation saccadic movement even in asymmetric convergence.

The stimulus that sets off a saccadic movement is the drift of the retinal image away from the fixation point, a fact which places saccadic movements under visual rather than propioceptive control.[31] However, experiments designed to elicit pursuit movements demonstrated that they were slow and smooth rather than the expected series of saccades. Does this mean there are two types of versions—saccadic, as one, and smooth, as the other?

The quantity of convergence reflexly associated with accommodation (A-C/A) is usually less if determined by maintaining a constant fixation distance while varying the accommodation stimulus with different-power lenses than that determined by varying the accommodation stimulus with altering fixation distances. The reason for this has troubled many investigators for a long time, so much so that the term proximal convergence has been designated to identify this intangible psychic awareness of nearness. This past year saw an attempt to measure the proximal convergence as a ratio with accommodation (P-C/A),[32] which somewhat complicates rather than simplifies the near-vision reflex. By using (1) the phoria technique (which prevents binocular vision) and (2) the fixation disparity technique (which permits binocular vision) and interpreting the experimental data by putting them through equations, the A-C/A and P-C/A were determined. The results were as follows: 1. The A-C/A ratio is stable and not easily susceptible to alteration by orthoptic training. (The ratio has been changed siginificantly by cycloplegic drugs [34] but insignificantly by phenylephrine [Neo-Synephrine] or a combination of 2% pilocarpine and 0.25% physostigmine.[35] My experience with isoflurophate [DFP] is quite the reverse of this last statement.) 2. Myopes have higher A-C/A ratios than hyperopes,[32] and this is attributed to their greater need for more convergence for each diopter of accommodation than that needed by hyperopes. 3. Convergence excess has a high A-C/A ratio, and convergence insufficiency is associated with a low ratio.

There are certain features open to criticism in the concept of the P-C/A ratio [32]

in general and in this investigation in particular. Concerning the latter, the authors were careful to point out in conducting their tests that an accommodative stimulus was offered, but the results were interpreted as though the full accommodative response had been made. Because the resolving power of the eye is so superior to the requirements imposed upon it in usual near seeing, and since the depth of focus of the eye is an additional factor, I doubt that the accommodation response is even close to the accommodative stimulus in all accommodative and proximal convergence studies conducted to the present time. Concerning the general criticism of the P-C/A concept, the very ground upon which is based the premise that a distinct entity of proximal convergence actually exists is unfirm. One interesting suggestion attempting to explain "proximal convergence" is that it actually is voluntary (frontal lobe) accommodation rather than reflex accommodation used to sharpen a blurred image (occipital lobe). And, regardless of the source of the accommodation innervation, there always is the associated reflex convergence innervation. Simply imagining that something is near incites accommodation.[33] Therefore, any psychic factor that brings forth accommodation, such as fixating a point in space known to be near, causes the accommodation response to be more similar to the accommodation stimulus. A careful electrical study of accommodative convergence failed to disclose any separate impulse for proximal convergence.[30]

A method of constructing a "dioptric coordinate" system which permits rapid evaluation of prism diopters of convergence associated with focal diopters of accommodation is presented.[36]

Some new facts that are appearing make me wonder about the possibility of there being a divergence reflex associated with distance seeing as compared to the convergence reflex associated with near seeing. For example: (1) Divergence has definitely been established as an active process, and (2) the inference is that a certain tone normally is present in the ciliary muscle, which is inhibited by the sympathetic system in order to clear the vision for distant seeing and is stimulated by the parasympathetic system for near seeing. The facts that support this inference are that (*a*) sympathicolytic drugs result in the eye becoming 0.5 to 0.75 D. myopic,[37] (*b*) cervical sympathetic nerve stimulation has increased the hyperopia and superior cervical ganglionectomy has caused a 1.8 D. relative myopia in a rabbit eye,[38] and (*c*) the totally color blind do not respond to accommodative stimuli but maintain a certain ciliary muscle tone that provides a false myopia even when they are looking at distance—comparable to the night myopia or sky myopia encountered in normal-sighted persons.[39] Since convergence is reflexly associated with parasympathetic stimulation, it is not too preposterous to wonder whether divergence is associated with sympathetic inhibition of the ciliary muscle.

Perhaps accommodation response is not so symmetrical (equal) as it is assumed to be.[40] In the unilateral myope, objective retinoscopy shows less accommodation for near vision in the abnormal than in the normal eye. In anisometropic hyperopia with amblyopia in the greater hyperopic eye, and in unilateral strabismus with amblyopia ex anopsia, the poorly seeing eye accommodated less. It is interesting that the squinting eyes relaxed accommodation for distant viewing more poorly than the master eye. The hypothesis is that accommodation is learned, but also it can be unlearned. For example, an eye with acquired blindness accommodated much less than its normal fellow eye. Also, the unequal accommodation provokes discomfort when full anisometropic correction is prescribed. If accommodation is a learned process, equal accommodation should be learned more easily by a child

than an adult; certainly a youngster more readily accepts full anisometropic correction.[41] In evaluating this research the fact that eccentric fixation often gives erroneous spherical and cylindrical findings[42] will have to be kept in mind.

Verhoeff 25 years ago apparently experienced doubt about a former belief as to the existence of Panum's areas, but with undampened spirit he forged on to develop his theory of replacement.[11] More recent experimental data continue to open fresh wounds in the theory of retinal correspondence. Photographic and direct telescopic observation had both found the eyes to be less converged by several degrees than was demanded by the targets used in this study. The disparity of the visual axes was significantly more than Panum's fusional space would allow for binocular single vision, and yet binocularity was undisturbed. The retort that saved the day for the retinal correspondence theory was the doubt cast upon the accuracy of techniques that employed photographic or telescopic observation of images reflected from the corneas.[43] The inference was that the whole eye shifted in the orbit (anterior-posterior and/or nasal-temporal) upon moving, which displaced the reflected image, giving erroneous findings. But new studies using electrical and entoptic methods which again attempt to reveal the amount the eyes are actually underconverged, and yet maintain binocular vision, after sudden interposition of a base-in prism before one eye give results compatible with the earlier photographic and optical studies.[44] The discrepancy between the actual convergence and the convergence required to overcome the prism was several degrees. The entoptic image used in this experiment was Maxwell's spot. This is a small dot seen only by the macula which appears while the subject is viewing an unpatterned purple background. The subject maintained binocular vision by fixating a plumb line in front of a purple background. When a base-in prism was suddenly interposed before one eye, Maxwell's spot remained centered on the plumb line. If the eye not behind the prism was suddenly occluded, momentarily the Maxwell spot was eccentric by as much as 1.7 degrees before a fixation movement recentered it on the plumb line. This indicated that binocular vision occurred despite the magnitude of eccentric fixation of the eye behind the prism.

The authors[44] conjecture about two additional expected subjective manifestations that should be explained on the basis of the lines of sight failing to intersect at the object viewed during prism vergence testing. 1. The perception of the viewed object becoming smaller and more distant as prism power is increased is suggested to result not from convergence per se but rather from an increasing temporal image disparity. This is somewhat related to a similar observed phenomenon reported earlier in this review (Roelofs and Zeeman[5]). 2. Reduction in stereoscopic acuity should be expected when the subject looks through base-in or base-out prisms, since "it is known that the locus of maximum stereoscopic sensitivity has a fixed relation to the point of intersection of the lines of sight, and presumably the stereoscopic sensitivity rapidly decreases on either side of this locus." Former researchers have demonstrated that stereoscopic acuity diminishes when a subject looks through base-out and base-in prisms.

Horizontal prism vergence amplitudes have been found to be highest when determined with Risley prisms, lowest with Berens prisms, and most variable with the synoptophore.[2]

Peripheral fusion is stronger than central fusion. That this is so was not questioned, but it was questioned whether peripheral fusion is stronger because a larger retinal area is stimulated or because the actual peripheral locus is superior to the central retina.[45] The tentative answer to this question is that the peripheral retinal locus, rather than the larger size of

the peripheral retinal area stimulated, provides the more powerful compulsion to fuse.

Asthenopic eyes have diminished visual acuity and peripheral field and an increased instability of fixation, as judged from the observed squinting and nystagmic movements and the changes shown on the graph of the electro-oculograph.[46] In short, the ability to see quickly and securely is diminished. The impairment is worse in amblyopic eyes,[47,48] but as vision improved under pleoptic treatment so did the asthenopic responses.

An apparatus (modified Müller's instrument) has been described for painlessly measuring the strength of the eye muscles.[49]

Analysis of rolling (false and true) associated with tertiary uniocular rotations is still being conducted. A scheme designed to convert the globe to a plane map was presented so that a better concept of the false torsion associated with the objective verticals could be grasped.[50]

Sensory Complications of Strabismus

Amblyopia.—Among certain groups of the population the incidence of amblyopia reaches 3%.[51] The importance of its detection long before school age is stressed. Unfortunately, the convention of conducting the first routine visual acuity testing in school makes this detection too late. A test is described that uses small colored grains of sugar; if they are seen at 5 to 6 ft., visual acuity of 20/60 is assured. Very young children can be tested. My experience is that most children possessing normal social adjustment and intelligence can be tested with the illiterate E-test at the age of 4. Furthermore, the prognosis is good that glasses and occlusion will establish good central vision in the amblyopic eye if treatment is started at that age. It should not be implied that treatment ought to be withheld if amblyopia is detected sooner.

Perception of form, brightness, and color are diminished in the central field of the amblyopic eye.[52] The degree of loss is proportionate to the duration of the amblyopia. The macula also shows a disappearance of alternating retinal function for form and color.[53] The disturbed retinal rhythm does not extend over the whole retinal area of the amblyopic eye; rather, it is confined to the macula. With restoration of good central vision, rhythm of alternating color perceptions becomes rapid and regular, as in the normal eye; also, the stereoscopic acuity becomes normal.[54]

The duration of time a normal subject can maintain fixation with the fovea is between 7 and 13 seconds, depending on nature of the fixation target.[55] The time is less in parafoveal fixation.

Pleoptic and surgical treatment of esotropia cases (either alternators or monocular amblyopes) caused the central scotoma of the deviating eye to decrease in size and intensity. Also, either a relative ring scotoma appeared in the fixating eye or diplopia developed.[56] The latter occurred before surgery with normal correspondence but after surgery with abnormal correspondence. This zone of inhibition (relative ring scotoma) that appears in the fixating eye during treatment is a fascinating phenomenon. The authors conclude from this, plus the improvement of the central scotoma in the deviating eye, that amblyopia is due to a functional inhibition at the retinal level. However, a different author reaches the conclusion that amblyopia is of central origin, since the light sensitivity responses were identical in amblyopic and normal eyes with the use of Adaptinol.[57]

In last year's review[29] I described the afterimage transfer phenomenon and indicated that some believed that it was a valuable test for prognosticating whether vision could be improved in an amblyopic eye. Unfortunately, I gave credit to Jaffe and Brock (1953)[58] for originating this test, when it should have been given to Brock and Givner (1952).[59] Brock and Givner found that 80% of alternating strabismus

cases could not transfer and hence saw no vertical afterimage following transfer of the cover from unstimulated to stimulated eye. Seventy-five per cent of unilateral strabismus patients could transfer, but only 20% of these could fixate centrally, after the transfer, with the amblyopic eye. Hauser and Burian [60] repeated the same test that Brock and Givner described and also reversed the test by stimulating the amblyopic eye directly with the vertical filament rather than the sound eye. Then they investigated the capacity of the amblyopic eye to fixate the target directly, and finally they studied the localization of the transferred afterimage in the sound eye. They could not confirm findings of Brock and Givner. The multiple factors of abnormal retinal correspondence, difficulties of controlling the patient's attention while he was fixating, uncertainties that even normal persons have in steadily maintaining a transferred afterimage, and difficulties of trying to encourage central fixation on such an unstimulating target as a black dot on a white test chart all add up to making the Brock-Givner test unreliable for determining the fixation pattern of the amblyopic eye. Nor does this test aid in concluding that amblyopia ex anopsia is primarily a sensory anomaly or primarily an abnormality of the motor function, as has been claimed (Linksz).[61] One of the major points made by Hauser and Burian [62] is that an amblyopic eye suffers a relative weakness of fixation—not an absolute one. The difference between eccentric and central fixation in amblyopia ex anopsia is one of degree only.[60,63]

A study relating anisometropia, binocular vision, and amblyopia revealed that 65% of anisometropes have binocular vision if the vision is normal in each eye, 35% have binocular vision in the event there is unilateral amblyopia, but 42% have binocular vision in the presence of bilateral amblyopia.[64] In other words, poor vision in one eye is more likely to cause strabismus than poor vision in both.

A plea is made to classify more carefully the types of fixation observed by ophthalmoscopy (Visuscope),[65] since Wertheim has previously presented visual acuity curves for different regions of the macula and surrounding area. Consequently, it would be more meaningful for purposes of conveying probable acuities to use the following terms: foveal, juxtafoveal, parafoveal, perifoveal, juxtamacular, extramacular, and parapapillary. Between the center of the fovea and the macular boundary the acuity drops from 1.0 to 0.4, and from the macula to the disc it drops from 0.4 to 0.16. However, since the nature of stimulus presented for fixation, as well as the attention given to the task of fixation,[66] introduces many variables, it is doubted that estimating the point of fixation by ophthalmoscopy can reflect the precise degree of visual acuity.

Last year's review gave Bangerter credit for developing the Visuscope as an objective means of determining fixation in the amblyopic eye. The error was kindly pointed out to me.[67] Actually, Bangerter used a small aperture in a disc over an electric ophthalmoscope and observed how the patient fixated this spot of light. Cüppers refined this method by projecting a small asterisk onto the retina, adding a green filter, and, while keeping the light intensity low, directly observing how the patient fixates the "star." Thus, the instrument that evolved was the Visuscope.

Some eccentric fixators cannot "find" the macula in the unsound eye even after prolonged occlusion of the sound eye. Euthyscopy, by producing an entoptic localization signal, actively helps these victims locate their macula. The entoptic phenomenon is nothing more than an afterimage created by this special ophthalmoscope (Euthyscope) shielding the macula while projecting a doughnut of light around it. The center of the afterimage is the macula. The ring afterimage is visible on a light illuminated background, first being seen as positive (illuminated ring with dark center)

and subsequently, as negative (dark ring with illuminated center). Much has been written about the difficulty of experiencing the negative afterimage when fixating with the amblyopic eye,[68] or at least amblyopia delays its appearance[69] and hastens its disappearance.[69,70] However, no relationship was found between duration of the negative afterimage and ultimate degree of improvement in the visual acuity with treatment.[70]

Optotypes have been the usual targets fixated with the illuminated center of the negative afterimage phase, but even this achievement does not guarantee foveal fixation. However, use of Haidinger's "polarization brushes" (available in either the Coordinator of Cüppers or the Macula Deficiency Tester of Goldschmidt) is an intriguing method for encouraging foveal fixation by entoptic phenomena.[68,71,72] I wonder if the Maxwell spot could be used to any advantage in this technique.

The ophthalmic literature continues to expand under the pressure of mounting reports concerning various experiences with Euthyscopic treatment. In general the claims are moderate—ranging from 0% to 100% success.[68-71,73-76] Five separate reports record how Euthyscopy aided visual development in the bad eye after sudden loss of the good eye.[68,70,71,75,77] In general, failures fall into the following categories: inability to appreciate the negative afterimage, patient too young or too deficient mentally to cooperate, and social circumstances preventing adequate attendance or cooperation.[68] This method, in large part, still falls short of attaining full visual acuity; the final acuity frequently rests around 6/24.[69]

The bad eye is occluded for a few weeks usually prior to starting the active Euthyscopic treatment[74] and between treatments until it is certain that macular fixation is established. This idea of decreasing the inhibition of the macula by occluding the bad eye has not been confined to those who practice Euthyscopy. One author did this to convert steady eccentric fixation to wandering fixation while simultaneously increasing the peripheral fusion with orthoptics so that peripheral fusion might more easily hold the eyes straight after surgery.[78] Another author met with uniform failure when trying to convert eccentric fixation to roving fixation by occluding the amblyopic eye.[79] He had hoped to switch occlusion to the good eye and obtain macular vision in the amblyopic eye after it had given up steady eccentric fixation.

In essence pleoptics differs from Euthyscopic treatment in that the visually stimulating exercises of pleoptics are designed to be executed by an orthoptic technician while Euthyscopy requires tedious prolonged ophthalmoscopy and requires an ophthalmologist. As Foster[68] puts it, "the adoption of his methods (Cüpper's Euthyscopy) must either require ophthalmologists to spend a much greater proportion of their time in the treatment of squint . . . or must require orthoptists to learn ophthalmoscopy." Pleoptics can definitely give a good result sooner than simple occlusion and homework exercises, but the question is raised as to whether it is justified.[80] The final outcomes of the two methods are not outstandingly different, but even Bangerter states that a child 5 or 6 years old requires anywhere from 20 to 120 treatments. But with the occlusion method, even if the child saw the orthoptic technician every two weeks over a six-month period he would make only 12 visits. So the old-fashioned, time-proven method of early and total occlusion is far from being abandoned.[63,80-83] I think that with simple occlusion at an early age, plus mass visual screening of all children between 4 and 4½ years of age, there would result within one generation such a scant number of monocular amblyopes of the ex anopsia type that little need would prevail for these expensive and noble attempts to improve amblyopia at a later time in life.

A well-documented report from the Wilmer Clinic bears out the futility of occlusion treatment for eccentric fixation in the adult (between the ages of 18 and 22). None improved beyond 20/200 vision with four weeks of occlusion, and in no case was centric vision established.[84] After instituting a technique of teaching macula location to these patients by directing a pantoscope macular beam onto the macula, secure macular fixation was established, with ultimate remarkable success resulting in two-thirds of those treated.

Caution is directed at interrupting amblyopia therapy too soon, i. e., before the result is well established.[85,86]

Burian remarked a year ago that in some patients the visual acuity is improved following surgical straightening of the amblyopic eye.[63] This probably is related to the observation that Visuscopic examination of the amblyopic esotropic eye reveals a greater degree of eccentricity of fixation in adduction and less in abduction.[87] Likewise, the vision was better in abduction than adduction, and surgical improvement of the alignment correspondingly increased the visual acuity in the primary position. The operator advised recession-resection of the amblyopic eye.

Hypnosis has been experimented with in the treatment of amblyopia in nine persons from 16 to 47 years of age.[88] Suggestions made under hypnosis to the effect they would be able to read with the poor eye after hypnosis, attempts to induce improvement in reading under hypnosis, and "age regression" techniques attempting to recapture the plastic functional status of childhood—all proved futile.

Suppression.—Just as there are differences between monocular central and peripheral vision so there should be differences between binocular central and peripheral vision. Earlier in this review the fact that peripheral fusional vergences are stronger than central fusional vergences was alluded to. Now additional facts point up this difference. Simultaneous perception is natural for the periphery but not for the macula.[89] The central scotoma outlined in the deviating eye during binocular vision may be completely eradicated whereas the peripheral suppression area is diminished in a transitory manner when the test subject inhales oxygen or receives amphetamine (Benzedrine) or strychnine by injection or per os.[90] Also, strychnine and intermedin in eye drops, either alone or combined, may have a similar effect. These results are attributed to better oxygenation, which combats synaptic blockage. Since eye drops give results similar to those of systemically administered medications, it is deduced that even in suppression of central origin there is also a peripheral factor. The reverse of this idea, e. g., the use of barbiturate drugs to enhance suppression in postoperative diplopia, is of little value.

Clinically, it seems to me that we are constantly confronted with this difference between central and peripheral fusion in the sensorial adaptations of suppression. For example, esotropia of 5△, plus or minus, with suppression confined to a small central area in the deviated eye, which may slightly impair its monocular fixation ability (visual acuity), is a frequent finding. The peripheral binocular vision is intact, but the central binocular vision (bifixation) is not. Two excellent papers on suppression appeared during the past year[90,91] which present the modern details of diagnosing and treating suppression, but in general no distinction is made between peripheral and central suppression and the individual problem each offers.

Diplopia training with red glass technique seems to be the standard approach to breaking down peripheral suppression, regardless of whether the squint is constant or intermittent.[88,90,91] Methods which employ physiological diplopia also are popular for peripheral antisuppression therapy, but this technique demands straight eyes. The following all require straight eyes and simultaneously treat central and peripheral suppression: bar-reading; advancement and

recession exercises while the subject is binocularly fixating a fixed object [89,91,92]; detailed work done with a red filter over one eye; exercising with the cheiroscope, stereoscope, television viewer with either Polaroid [92] or color-filter arrangement,[94] and the Correct-Eye-Scope.[94] The old trick of using string is redescribed.[91] As an exercise, it simultaneously attacks central and peripheral suppression, and in addition it is capable of increasing the fusional vergence. The eyes may be esotropic while doing the exercises. A 6 ft. string extending from the patient's nose to a stationary object is intersected at some point by the converged visual axes. Bifoveal fixation of a pencil held at this point causes the proximal portion of the string to be perceived as separate converging strings (physiological heteronymous diplopia). The distal portion appears to be separate diverging strings proceeding away from the pencil (physiological homonymous diplopia). Since the esotrope is apt to suppress the nasal retina, homonymous diplopia (distal portion of string) is likely to be suppressed by the deviating eye. Moving the pencil forward and backward along the string requires fusional vergence if the pencil is not to be seen as double, and proper physiological diplopia is maintained for the proximal and distal portions of the string.

Advantage of the stronger peripheral fusional vergences is taken in the suppression treatment that uses amblyoscope slides which project large rings on the peripheral retina.[78] The technique overcomes peripheral suppression and increases peripheral fusional vergence amplitudes. If central suppression or amblyopia cannot be overcome, the merits of this technique are all the more appreciated. In fact, this technique is advised before starting and during amblyopia treatment in order to prevent occlusion tropia. But the actuality of occlusion tropia being a significant clinical problem is questioned.[79]

A very sound note has been struck by pointing out that vergence fusional amplitude means little unless it is analyzed for both speed and endurance.[95]

The blind spot syndrome and its built-in peripheral suppression feature is brought up again.[90] A warning is issued about inadvertently trying to eliminate the area of suppression in the deviated esotropic eye that measures and localizes as the papilla.[91]

An ophthalmologist reporting on 50 cases of strabismus is pleased with the results of occlusion.[97] After amblyopia is overcome, binasal occlusion in esotropes and alternate occlusion in exotropes is started. This establishes a secure alternation and prevents the susceptible retinal area of the nonfixing eye from receiving the stimulus to suppress. Following surgery, more monocular patching is done. With good surgery and glasses fusion may spontaneously ensue. It is suggested that orthoptic training be reserved for those who fail to develop fusion by the above routine.

Abnormal Retinal Correspondence.—A study of the visual fields in strabismus patients was made in the following manner: (1) monocular scotometry, (2) binocular scotometry after an adjustment had been made for the misalignment in order to provide an assessment of the sensibility of corresponding points during binocular vision, and (3) binocular scotometry of the mutual relations of the two fields of vision that overlap, no adjustment having been made for the misalignment.[98] Two techniques were used—complimentary colors and polarized light. Closely related to this was a second report about the binocular vision in strabismus with no adjustment for the angle of squint.[99] Anaglyphic glasses (red before one eye, green before the other) were worn while the subject was viewing an unmarked well-lighted white screen.

The normal nonstrabismic person experiences a mixed red and green color with some various degree of color rivalry, never seeing the screen as in monocular vision, when it is either bright red or green.[99]

Patients with acquired esotropia and exotropia, having good visual acuity in each eye and normal retinal correspondence (NRC), see the screen as double. The parts of the screen that do not overlap are seen as a pure color, areas of pure color being uncrossed in esotropia and crossed in exotropia. The overlapped part of the screen is seen as the normal person sees it.

If there is NRC but deep amblyopia of the deviated eye, the central part of the screen is seen as the pure color of the filter before the fixating eye. Binocular scotometry with adjustment for squint angle reveals in the highly amblyopic eye a vast area of deep suppression encompassing its fovea.[98] The same scotoma is present on monocular scotometry. Binocular scotometry not adjusted for the squint angle shows the central field of the fixating eye to be intact, but the islet that compares with its blind spot is seen by the amblyopic deviating eye.

Binocular scotometry conducted on alternators (I presume with ARC), with no adjustment having been made for the esotropia, that ranged from 12 to 20 degrees, indicates that the blind spot of the deviated eye becomes modified in shape, more or less according to the needs determined by the size of the squint angle, in order to neutralize (suppress) the image that projects onto the macula of the fixating eye.[98] Similar patients examined with anaglyphic filters saw the right third of the white screen with the deviating left eye and the center and left thirds with the fixating right eye.[99] The exotrope with ARC sees the left third of the screen with the deviating left eye while the fixating right eye sees the middle and right thirds. If a vertical deviation is combined with the horizontal, the rule is that part of the screen viewed by the fovea will be seen in the color of the filter worn over the fovea and the division of the color field will be along an oblique axis. If ARC is associated with unilateral amblyopia, the entire screen is seen in the same hue and intensity as the filter in front of the fixating eye.

Contrary to what might be assumed from these investigations, the patient with ARC does not have monocular vision for certain divided areas of his field.[99] Small red and green targets are seen by ARC patients as demonstrating divided color field phenomena in all parts of the field. In other words, small green targets projected onto that part of the screen that is seen as red with the right eye are instantaneously seen with the left eye, and vice versa. From these studies it is hypothesized that in ARC the deviated macula is dominant over the peripheral retina of the fixating eye for perception of different stimuli of equal intensity. It is further suggested that this simple procedure can be used for diagnosing ARC. A divided color field phenomenon indicates ARC, but its absence does not indicate NRC, or the absence of ARC.

That the type of stimulus presented and the power of suggestion accompanying ARC testing cause considerable variability in the findings is the conclusion of one who did intensive investigations with the haploscope and binocular perimetry with color and polarized light.[100] He theorizes that NRC is not innate or immutable but develops day by day as the child matures. In the same way, the two fixed monocular fields become related to one another abnormally while formulating binocular vision habits which adapt for the angle of squint. The result is ARC.

Facts are facts, but there is no limit to the nature of interpretations you can apply to explain them. To illustrate, one author[101] found that among 600 patients with strabismus 194 exotropes and only 45 esotropes had ARC. And heretofore ARC and exotropia have been thought to be almost mutually exclusive.[102,103] Moreover, constancy of squint angle has been widely accepted as one of the usual features attendant on ARC; yet this author[101] claims that 73% of the exotropes had intermittent

ARC, manifesting NRC with eyes straight and ARC with eyes divergent. The angle of exotropia in 70% was between 20 and 24 degrees. The cause of the squint was attributed to the 20-degree divergent angle of anomalous correspondence. This led to the deduction that some patients have innate coexistence of NRC and ARC. When innervation is put forth to move the eyes into the ARC seeing position, the innate ARC competes with NRC. Another report[104] concerns intermittent congenital strabismus in an 18-year-old girl with both NRC and ARC. The suggestion follows that possibly all cases of intermittent tropia manifest NRC with eyes straight and ARC with deviated eyes.

Monocular diplopia has attracted considerable comment this year.[91,102,105-107] However, all agree that it signifies dual spatial perception by a single retinal element in a patient with ARC. It may occur after surgery or during orthoptic investigation or treatment. In fact, the modern routine for teaching NRC by the orthoptist revolves around getting the patient to recognize monocular diplopia and then teaching him to retain the proper and reject the anomalous image. Monocular diplopia can be accomplished in two ways by bifoveal stimulation. One may have the esotrope fixate a light through prism power that almost corrects the angle of squint. This results in widely separated crossed diplopia images. A red lens will identify which image belongs to which eye. Encourage him to concentrate on seeing one red and one white light very near to each other without moving his eyes. When it appears, have him hang on to it and teach him to mentally throw away the more removed image.[91] The second method involves use of the major amblyoscope. The patient either bifoveally fixates small dissimilar targets or fixates with the usual deviating eye while the machine is set at the subjective angle. This alone is often sufficient to evoke a transient monocular diplopia.[102] These two methods offer an initial central-vision attack on ARC prior to expanding to the peripheral areas.

Other authors have found success in treating ARC by first breaking through to the stronger peripheral fusion rather than going forthright to the macular area.[78,91] With use of large stereoscopic targets, stereopsis and peripheral fusion have been recovered in ARC patients long before simultaneous macular perception was obtained with dissimilar targets.[78]

If the above-described technique of monocular diplopia inducement on the major amblyoscope is used in the treatment of ARC, the everyday seeing must be switched to the nonpreferred eye. This means patching of the good eye when it is not being exercised.[102] Monocular diplopia training is not attempted before the age of 5. Prior to that age, occlusion is the only treatment, and its effectiveness is proven by the fact that by the time the child reaches the age of 5 usually no ARC is found. This author apparently has the same wholesome attitude about diagnosing ARC as the British. A difference between the objective and subjective angle of deviation does not necessarily indicate the presence of anomalous correspondence.[102] A variable subjective setting of the amblyoscope with crossing over of images at different points on repeated attempts is considered to indicate unstable binocular vision rather than ARC. Stable localization of the lion in the cage at an angle less than objective angle, a small range of fusion at the subjective setting, and a consistently abnormal afterimage test are the British ARC requirements.[108] Lack of NRC is described by them as the inability to put the lion in the cage due to the crossing over at various angles less than the objective setting and an absence of any fusion range, and the afterimage test may be normal or abnormal.[108]

About 80% of 106 real cases of ARC definitely diagnosed in patients over 4 years of age were corrected to permanent

NRC.[102] These are truly remarkable results, particularly when it is realized that in some areas treatment of ARC is no longer practiced,[79,109] because of the universally poor results. A carefully worked up report from the Moorfields Eye Hospital, London, reveals 100% failure in treating 16 cases of ARC.[108] The possibility of orthoptics converting lack of NRC to NRC is somewhat more favorable, since 27 of 72 cases classified as lack of NRC attained NRC.

Surgery is recommended for ARC,[110] but since there is a tendency to slip back into the previous squinting position, pre- and postoperative orthoptics and occlusion are advised.[111]

Heterophorias

Weak simultaneous macular perception in otherwise normal eyes is thought to be the cause of many instances of headaches, nausea, and discomfort.[112] Of 255 cases 93 patients were orthophoric and 162 were heterophoric. The symptoms were relieved by stimulating the fusion sense, and the deduction is that weak bimacular perception is the cause of the heterophoria. It is postulated that even those cases that are orthophoric at present would become heterophoric in the future if left untreated.

Convergence insufficiency is the commonest of all phorias.[113] Often those with the most marked findings are more comfortable than others with insufficiency of more moderate degree.[113,114] Improvement is available to most if they will undergo a simple training program. However, this program should be carried out in logical sequence, as the following illustrates[115]: 1. Maintain bifixation on a white-headed pin placed on a cardboard separator for a count of 100. Inch by inch, place the pin nearer to the nose while holding bifixation for the full count. When fusion can be held with the pin 1 in. from the tip of the nose, progress to Step 2. 2. Perform pin- (or finger-)-to-nose and pencil-point-to-pencil-point exercises (the orthoptist or whoever assists with the exercises at home holds one pencil horizontally with the point 12 in. in front of the nose. The patient, holding an opposing pencil, attempts to make the points touch. As the pencil is varied slightly in distance for each pass the patient makes in contacting the points, good stereopsis is demanded, and this means bifoveal fixation plus convergence. In a gradual manner this exercise is carried in closer to the nose). 3. Voluntary convergence, such as looking at the tip of one's nose can be accomplished after mastering finger-to-nose and pencil-to-pencil exercises. In addition to this routine, other things can be done, such as exercises with loose prisms of gradually increasing power. The television trainer provides a good fixation target for exercises with loose prisms.[116] Use of a home stereoscope is fine after voluntary convergence is learned.[115] Convergence exercises on office instruments, such as the major amblyoscope and the rotoscope, are helpful. Success should not be claimed until the convergence amplitude has been built up to 70 D. on the major amblyoscope or 50 D. as measured by loose prisms for both distance and near fixation.

In general, the intent of treatment in convergence insufficiency is to increase the positive relative convergence[113] (convergence amplitude measured while the accommodation remains fixed, e. g., determination of amplitude during reading of fine print). Obtaining improvement that satisfies this stricter standard of measurement is often more difficult than one might think.* Suggestions from three different authors for mastering this impasse are the following: 1. Gradually add clip-on minus lenses, which induce accommodative convergence, and after −4.00 sph has been mastered the patient usually converges unassisted.[117] 2. Initially use large peripheral stereopsis targets on the troposcope, thus taking advantage of the stronger peripheral fusion and, once realizing how a powerful

* Eustis, A. T.: Personal communication to the author.

convergence movement feels, the patient will understand how to reproduce it when fixating a foveal target.[78] 3. Produce forced contraction of the lower lid portion of the orbicularis, which is associated with the synkinetic near reflex.[118] An assist by this method while one is encouraging convergence on a near point may get the patient started who cannot discover how to converge otherwise.

Not all patients are helped by orthoptics. By no means are exercises automatically indicated for all persons suffering symptoms attributable to convergence insufficiency. Orthoptics are preferred for the young, but prisms should be considered for those more than 40 to 45 years of age.[119] If there is no exophoria at distance, then only prismatic near glasses are needed, or if bifocals are used have the prisms placed in the segments. Surgery is reserved for those who have a large phoria at distance and receive no comfort from prisms.[114,119]

Divergence insufficiency is seldom aided by exercises, and usually the deviation at distance is too great to be helped with prisms.[119] Consequently, surgery is advised,[113,120] but, first, time should be permitted to show its effect on the malady, since a systemic illness frequently is associated, and both may spontaneously improve.[119] If prisms are attempted they are necessary only for distance (distance glasses with prisms or clip-on prisms over regular glasses).

Divergence excess is best handled surgically for all except those with excess of small degree, for which orthoptics may be tried.[114,119]

Hyperphoria of more than 1 D. deserves a trial of prism correction, granted there are asthenopic symptoms.[119] The phoria measurement used in prescribing the vertical prism in larger degrees of hyperphoriatropia should not be a red glass determination (I presume this also includes Maddox rod), since this eliminates all fusion (peripheral and central), which would likely result in an unnecessarily strong prism being ordered. A better method is to merely weaken the peripheral fusion somewhat by lowering the illumination and prescribe the prism required to elicit fusion when the patient is looking at test letters. For the small hyperphorias it is best to size up the vertical vergence amplitude against the hyperphoria measurement (method of measurement is not indicated) and prescribe the prism power that allows an equal distribution of the vergence amplitude when this is measured through the correcting prism. Still there remains the fact that sizing up a patient's response to prisms and determination of the ultimate minimal prism power that affords comfort is fickle business. No apologies are due from those who habitually use the unscientific clip-on trial prisms.[117,119]

Hyperphoria should be checked without corrective lenses (inadvertent decentration of lenses introduces error), red lens over dominant eye (patients automatically fixate red better than white), white Maddox rod and compensating prisms over nondominant eye (patients have tendency to not fixate with eye behind prisms), at distance and near with eyes depressed 20 degrees during near testing.[121] The difference in phoria produced by moving eyes out of the primary position has been called anisophoria. Depressing eyes while seeing at near through anisometropic lenses induces vertical anisophoria, but often there is an opposing intrinsic anisophoria that reduces the resulting net anisophoria to within the zone of tolerance. Consequently, no optical compensation should automatically be prescribed for the induced vertical anisophoria at near without first studying the near intrinsic anisophoria.

Accommodative Esotropia

Hypermetropia, important as it is etiologically to accommodative esotropia,[122-125] apparently is the primary factor in only about one-half of the cases.[126] Since the other half have normal ranges of hypermetropia and overconvergence at near fixa-

tion resulting from an unsolved etiology, an open invitation persists for explaining this phenomenon. Insofar as the ophthalmic literature for the past year can be used to measure the volume of thought being consumed by this complex and prevalent clinical problem, I judge that this open invitation is not left unheeded.

The current theories advanced to explain hyperconvergence at near all embrace the concepts that (*a*) a discharge of motor innervation to the ciliary muscles sets off the sequence of events and (*b*) reflexly associated with this accommodation impulse from the visual cortex is a simultaneous discharge of motor innervation to the medial recti. Where opinions first split that attempt to explain this disorder is at the level of whether the reflex association of accommodation and accommodative convergence is innervationally normal or abnormal. The following classification covers current theories.

I. Normal reflex
   (*a*) Inadequate accommodative response, e. g., weak ciliary muscle
   (*b*) Overaccommodation
   (*c*) Infantile (relatively small) interpupillary distance
   (*d*) Infantile latent hypermetropia resistant to being disclosed with cycloplegia
II. Abnormal reflex

The poor accommodation hypothesis has two variants. The first is Costenbader's suggestion of a reduced accommodation ability as measured by remote near point of accommodation.[122,123,127] Such an assumption implies that excessive accommodation is required for clear vision, which in turn is associated with hyperconvergence. The fact that practically all observers measure normal monocular and binocular accommodation amplitudes on these patients defeats this suggestion. The second and very stimulating idea concerning hypoaccommodation is based upon the observation of the frequency with which bilateral overaction of inferior obliques and underaction of superior obliques, plus V-type esotropia, happen to occur in conjunction with exaggerated esotropia at near.[127] The thought is that, since motor impulses to the ciliary muscles course along fibers of the oculomotor nerve branch that innervate the inferior oblique, prior to departing by way of the ciliary ganglion to the eye, some accommodation impulses might overflow to the inferior oblique muscle. If the ciliary muscles are originally weak, extra effort must be put forth to clear the vision, and this is associated with overaction of the inferior obliques and hyperconvergence. In depressed gaze (the common position for accommodation) the inferior oblique contraction might be sufficient to embarass the superior oblique vertical action. This suggestion is an attempt to solve not one but three related intriguing problems: (1) hyperconvergence at near, (2) overaction of the inferior obliques, and (3) V-type esotropia.

Overaccommodation at near and its associated overconvergence is another consideration[123] designed to explain the high degree of esotropia at near that some accommodatives manifest. Since approximately 2 D. of overaccommodation can be compensated for by depth of focus of the eye, it is conjectured that the induced myopia would not automatically blur the vision but that its effect on the ocular alignment would be apparent. However, if this hyperirritable near reflex was elicited only upon near gaze, why would these same patients tend to have esotropia at distance in the presence of uncorrected small hypermetropia? Moreover, why should these patients so often have straight eyes at near when fixating a light (which presents no challenge to accommodate) but develop marked esotropia upon identifying a small letter or picture? Is it not plausible to expect a hyperirritable synkinetic near reflex to manifest itself regardless of the accommodation stimulus? In fact, I should think that enforced inhibition of accommodation at near would be more likely upon changing the fixation target from a light to a letter, assuming there to be overaccommodation for near seeing. Spasm of the near reflex is a very well recognized

clinical entity, characterized by induced myopia, miosis, and marked convergence found principally in young women and usually having associated psychic findings, which causes it to be classified as a functional disorder.[128-130] But this rare type of accommodative esotropia in adults is difficult to relate to a possibly weaker variety of the same condition being the cause of the common overconvergence at near in little children.

Another possible explanation is that the prism diopters of accommodative convergence reflexly associated with each diopter of accommodation remain the same throughout growth.[122,123] If the ideal relationship of accommodation and convergence that provides clear vision and perfectly aligned eyes is attained at full growth, then the narrower interpupillary distance of childhood will result in relative overconvergence at near. Granting a 2 cm. increase in interpupillary distance between the ages of 2 and 16 years, this could only account for a decrease by 6△ of the overconvergence at 13 in. Therein lies the weak point of the thesis, because the degree of overconvergence at near in these esotropic children is from 2 to 10 times that amount.

Latent hypermetropia resistant to being disclosed by cycloplegia is also set forth as a factor that might have some relationship to the overconvergence in near vision.[123] The reasoning behind this is admitted to be the recognized failure of obtaining absolute cycloplegia and consequent full disclosure of the total hypermetropia in children. I fail to understand how undiscovered latent hypermetropia could evoke compensatory accommodation only at near and not at distance. Consequently, the possibility of overconvergence at near resulting from such a factor is considered to be groundless.

The last seriously considered explanation is that some unknown factor in the form of either excessive or inadequate central synaptic resistance allows an imbalance in the flow of impulses effecting accommodation and accommodative convergence—an imbalance of the type that results in a preponderance of convergence which is increasingly apparent the more the patient accommodates.[122,126] Minor transient changes from day to day in the overconvergence at near and major permanent changes over a period of years are compatible with the abnormal reflex theory. Fatigue, illness, emotions, and probably certain drugs transiently worsen the abnormal reflex, whereas maturation of the patient is associated with a gradual, but permanent, improvement in the abnormal reflex.

The important issue is to ascertain the type of variable defect present rather than the precise measurement by some cumbersome technique,[131] especially since these measurements in accommodative esotropia with overconvergence at near are subject to variation. The treatment of this type of accommodative esotropia is essentially no different from that caused by hypermetropia. Prompt and thorough curbing of the accommodation impulses to a degree commensurate with controlling the alignment of the visual axes is demanded, even if it means more than glasses that neutralize the total ametropia. Isoflurophate (Floropryl),[124, 132-134] pilocarpine,[135,136] and Mintacol,[137] have all been tried in place of glasses for accommodative esotropia, but almost everyone concedes that medication control in the long run is second-rate in comparison with glasses. However, in the event the overconvergence at near causes esotropia but the eyes are straight at distance some ophthalmologists rely on medication to curb the accommodation further, assuming glasses are worn,[138] rather than accept the claims of others who extol the virtue of bifocals.[82, 124,125] The objections to bifocals are expense, parental resentment, and possible eventual need of dissociation exercises anyway.[138] I feel that the over-all expense to the patient is less with bifocals, since the patient does not have to be examined so frequently, and I find that most parents tire of instilling drops and that some come to welcome an easier method for controlling

the hyperconvergence of near vision. Finally, a most resounding condemnation of all optical techniques designed to curb accommodation is the following from a Britisher's pen[139]: "The full or over-correction of the refractive error over a long period by glasses and in some cases by the use of bifocals is thoroughly bad medicine, because the normal growth of the ciliary muscle is retarded, and in some cases actual weakness may be caused by relative disuse." Actually, the last clause points up a frequently overlooked fact which if watched closely can be used to considerable benefit but if neglected results in exotropia. For example, an esotrope was still esotropic by a small amount shortly after glasses were prescribed, but as the years passed the eyes straightened.[140] This case must be watched closely, and at the appropriate time the power of the glasses must be lowered to avert exotropia. If neglected, exotropia is very likely to replace esotropia,[141] particularly if there is a poor type of binocular single vision or a hypermetropia of 6 D. or more.[123]

A residual esotropia still present after accommodation has been curbed is usually a surgical problem,[108,124,126] but only for that amount of esotropia measured while the patient is fixating at distance with glasses on. Fortunately, the abnormal overconvergence for near vision, if present, usually can be controlled optically or medically and improves with time.[123,124,126,127,142] However, if it is not controlled a small bilateral medial rectus recession is advised.[124] For a similar problem (small esotropia at distance and greater at near) recession of the medial rectus of the preferred eye is recommended.[142] The philosophy of another surgeon appears to be that of avoiding surgery for the residual esotropia of near unless the suasion of the parents dictates otherwise, owing to the great chance of converting the problem to exotropia of the divergence excess type.[143] Surgery is a most dramatic but unfortunately a very dangerous method for treatment of the overconvergence at near vision. It is unjustified unless a sizable and bothersome esophoria is present while the patient is fixating at distance with the accommodation curbed.[126]

Orthoptics[124,126] and a brief routine of isoflurophate used in gradually diminishing strength[126] increase the fusional divergence[122] amplitude in a more mature child (over 7 years old) so that the power of the glasses can be reduced or their use can possibly be discontinued. Clip-on minus lenses facilitate an everyday evaluation of determining whether the patient is ready for a lens reduction.[117,124]

Nonaccommodative Esotropia

Instead of diplopia resulting from esotropia, it is theorized that esotropia results from diplopia. The diplopia is purported to be caused by defective maturation of binocular vision, to the extent that only monocular vision is possible.[144] Double monocular vision (diplopia) is compensated for by deviation of the eyes, inhibition of the visual function in a certain area of the retina of the deviating eye (amblyopia and suppression), and ARC. If the inhibition attempt in the deviating eye is successful, diplopia vanishes, thereby removing the stimulus that causes the response of deviation. Hence, the eyes tend to straighten. If the inhibition is unsuccessful, as in alternating strabismus, the maculas persist in their competition for fixation and diplopia continues to provoke deviation.

This idea of defective maturation of binocular visual reflexes cannot be discounted by any of the following observations: 1. Of 300 children with concomitant strabismus 45% suffered cerebral trauma during delivery, 8% had a head injury, and 6% were ill with a systemic disease immediately before the onset of strabismus; 60% of the 300 had retarded motor responses and abnormal electroencephalographic findings.[145] 2. Forty-three per cent of children with cerebral palsy have strabismus, the cases being evenly divided between esotropia and exotropia.[146] 3. Of all patients with squint,

47.5% belong to families containing two or more members with this condition.[125] Stuttering, nystagmus, mental retardation, left-handedness, and innervational squint are linked together—one member of the family showing one feature while a second may manifest another.[125]

The bony orbital walls were studied by x-ray to determine whether the angle that the lateral orbital wall makes with the nasal wall, the median sagittal line, or the lateral wall of the opposite orbit has any relation to strabismus.[147,148] The only significant trend discovered was that the angle between lateral and nasal walls of the orbit containing the monocular strabismic eye was smaller in esotropia and larger in exotropia. The angles were equal in alternating strabismus.

A few cases of concomitant esotropia may start with otitis media which causes a transient weakness of one lateral rectus. Rapid contracture of the homolateral medial rectus and easy adaptive phenomena of suppression and ARC quickly lead to establishing a degree of comitancy that resembles the typical esotropia of infancy.[149] This is very unlikely in adults, owing to the persistence of diplopia, although there are many rare factors that do cause acute onset of esotropia in older children and adults. Heredity, neuropathic disorders, and endocrine disturbances predispose the patient to some more trivial cause setting off the tropia, such as trauma, diminution of the fusional powers, convergence spasm, and weakening of the divergence center.[149] There probably are a latent esophoria and unstable fusion, and the trauma of an emotional upset precipitates the sudden large esotropia,[150] its large angle of deviation being explained in part as an escape from diplopia, since widely separated images are less annoying.[151] An unfortunate incident is recorded of a 9-year-old child whose esotropia became permanent one hour after the eyes were atropinized.[152]

Convergent strabismus associated with hyperlaxity of the joints, tightly stretched skin, scoliosis, umbilical hernia, and flat feet constitutes an atypical form of the Ehlers-Danlos syndrome.[153] Histologic examination of the extraocular muscle tendon biopsy specimen showed significant alterations in the elastic fibers and collagen.

A photographic method of measuring squint has been presented.[154] Essentially it is an attempt to microscopically quantitate the squint angle as elicited by corneal reflex, rather than to estimate the angle by the Hirschberg method.

Currently, the most popular aspect of strabismus to write about is the importance of early surgery in nonaccommodative esotropia.[114,144,155-162] No author offers any method of treatment that excludes surgical correction of the misalignment. The differences in the reports are found only in the recommended therapy ancillary to surgery (occlusion, orthoptics, optical aids), the age at which treatment is given, the nature of the surgery performed, and the results attained.

The prognosis can be made as to the quality of binocular vision that is obtainable by orthoptics by evaluating the following factors: (1) age of patient, (2) age at onset of strabismus, (3) mode of onset (intermittent at onset or not), and (4) duration between onset and straightening by surgery or glasses.[108] The age of onset factor in nonaccommodative esotropia is most important. Those cases of early onset (birth to 18 months) are too poor a risk to treat with orthoptics unless the eyes were straightened within the first 2 to 2½ years of life. The prognosis of orthoptics benefiting the group with later onset is excellent.

In a similar way, another author divides the cases of squint into two groups according to age of onset.[159] If the onset of squint is prior to the age of 3, surgery is done as soon as measurements are reliable. If it first appears after 3 years of age, orthoptics is recommended for three to five months prior to conceding the necessity of surgery.

The initial operation preferred by most surgeons is recession of the medial recti.[114,160,163] For small deviations it is better to do

a small bilateral recession of 2.5 mm. than to attempt to achieve full correction by a larger amount of surgery on one muscle.[114] The recession procedure lends itself well to readjustment of the insertion if the result indicates that this is necessary.[161] Resection and advancement of the lateral recti combined with a recession of one medial rectus is the procedure of choice of one surgeon.[162] Advancements are objected to because the cosmetic appearance may be spoiled by a bluish shadow through the conjunctiva.[161] The importance of preserving convergence is stressed, and it is felt that medial recti recessions are safe for young children, but after the age of 6 the risk of weakening convergence demands caution; consequently, lateral rectus resections are preferred for the older children.[164]

Complications of muscle surgery are reviewed, such as severing the inferior oblique inadvertently when operating on the lateral rectus [165] or cutting a hole into the sclera when the tendon is freed from the globe.[165,166] Ischemia of the area supplied by the anterior ciliary arteries may be caused when they are cut.[166,167] Patients who had all four recti severed (Hummelscheim operation with resection of the lateral rectus and recession of the medial rectus) developed subacute iridocyclitis which resulted in depigmentation and atrophy of the iris.[167] Consequently, it was advised that no more than two recti be operated on at one session.

The important points in the Hummelscheim technique are recession of the medial rectus and transplantation of only the temporal halves of the vertical recti (not moving the nasal halves somewhat temporalward). Resection of the atrophic lateral rectus is unimportant.[168]

An offshoot of the tucking technique is described as a torsion procedure.[169] Instead of folding the muscle in an orderly way, as is done in tucking, one rotates the muscle belly 180 degrees while it is on the tucker and places a ligature at the base of the muscle loop produced by the torsion. In Russia, for a high degree of esotropia an operation is performed which entails a "careful" tenotomy of the medial rectus plus passing a suture through the stump, forcefully abducting the eye, and tying the suture around the ear.[170] A severe reaction ensues, and the suture is removed on the fourth day.

The small residual deviation of less than 10 degrees constitutes a difficult problem. If there is ARC or poor binocular function at this small angle, no surgery should be done.[114] If fusion ability exists, orthoptics may increase the amplitude and ultimately help the patient.[171] If this is unsuccessful, more surgery should be done rather than risk the development of ARC, which is greater than the risk of producing postoperative divergence, because the latter can be corrected surgically but the ARC becomes permanent after a time.[171]

Fixation Disparity

Intersection of the visual axes at the point of regard is bifixation. Fixation disparity designates the physiological deviation away from bifixation within the limits permitted by single binocular vision.[172] A minimal deviation from bifixation is as physiologically related to normal binocular fixation as physiological nystagmus is to normal uniocular fixation. Like physiological nystagmus, whose excursions are minute in normal fixation, fixation disparity is very small in normal binocular fixation. The upper limit of deviation of the visual axes from bifixation, as measured by the subjective test of freedom from diplopia, is in the neighborhood of 15 minutes of arc.[173] However, objective analyses employing photographic techniques have recorded values up to 2.4 degrees. Earlier in this review I alluded to the charges made against the accuracy of the photographic technique [43] and the counter charges supporting its accuracy based on closely correlated findings obtained by electrical and entoptic studies [44] (see Basic Science, Motor).

Horizontal fixation disparity and horizontal phoria are related. As horizontal prism power is increased before a patient with normal binocular vision an increasing fixation disparity develops, since the visual axes lag behind rather than make the full vergence movement to provide bifixation. Moreover, a phoria patient tends to have a disparity of the visual axes in the same direction as the phoria (e. g., in esophoria there is a convergent fixation disparity).[172]

Regardless of whether the physiological disparity of the visual axes can be measured in minutes or degrees, the average clinician probably has been guilty of semantic impurity, since stretching of the term fixation disparity to cover a naked tropia has been common practice. That large group of cases characterized by a small cosmetically acceptable deviation, manifesting peripheral but no central fusion, due to a small suppression area inhibiting the deviating macula, a slight unilateral amblyopia except in alternators, and defective stereoscopic acuity actually have small angle tropias rather than fixation disparity. The young patients of this category may have their amblyopia overcome with occlusion, but improvement in their monocular fixation skill does not alter their habit of suppressing one macula in ordinary binocular fixation.

Divergent Strabismus

Among 170 strabismus cases about 38% of each of the esotropes and exotropes had an average degree of pigmentation, characterized by brown hair and blue eyes.[174] In either the group having lighter pigmentation or the group having darker pigmentation, the percentages of persons with convergent and divergent strabismus were interestingly different. Approximately 44% of the exotropes were lighter and 19%, darker than average, whereas 23% of the esotropes were blonder and 39% were more brunette than average. This suggests an association between paucity of pigment and exotropia.

Overacting obliques in exotropia are presumed to be secondarily shortened as a result of a primary slackening of the obliques that occurs in an abducted eye (abduction offers a shorter distance between the trochlea and insertion of the superior oblique or the origin and insertion of the inferior oblique).[175] This concept is hard to reconcile with the frequently observed overaction of the obliques in esodeviation.† The contracture may be unequal, and either the inferior or the superior oblique may manifest hyperfunction in its vertical field of action.[175] The generalization is made that the exotropic eye may be elevated in divergence if contracture of the inferior oblique predominates and depressed if contracture of the superior oblique predominates. But I question this, since the divergent eye is in the torsional rather than in the vertical field of action of the supposed shortened oblique. Some patients with a very large degree of exotropia had restricted passive adduction as revealed by traction test, even after the horizontal recti had both been detached from the globe.[175] After freeing of one or both obliques, the passive adduction was enhanced.

Overaction of the superior obliques is frequently associated with A-type exotropia, characterized by an increase of the exodeviation on midline down gaze and decrease in up gaze.[175] Overaction of the inferior obliques is associated with V-type exotropia, i. e., increase in exotropia on up gaze and decrease on down gaze. Tenotomies of the superior obliques improved the A-type by reducing the difference in exodeviation between up and down gaze an average of 45△.[175] Resections of the inferior recti accomplished a change of only 18△. Bilateral inferior oblique tenotomies decreased the V-type by approximately 15△, the improvement in exodeviation being confined entirely to the up-gaze position, with little effect produced in down gaze.

A-type exotropia is attributed to paresis of the inferior recti, and resections of the inferior recti are advised.[176] The V-syndrome is blamed on weakness of the super-

† Burian, in discussion on Jampolsky.[176]

ior recti, and similar surgery is performed on these muscles. Another surgeon shifts the vertical recti (I presume the inferior recti in the A-syndrome and the superior recti in the V-syndrome) nasally by half their width to counteract the overacting obliques.[177] This recommendation is made despite the admission that possibly a factor other than paretic vertical recti, such as an abnormal insertion of the superior or inferior oblique, is the cause of the A- and V-syndromes. Electromyographic investigations in A-type exotropia have demonstrated in some cases increased firing of the lateral recti on down gaze with inhibition of the medials. In V-type exotropia the lateral rectus firing is increased in up gaze.[25]

It is advised that the lateral recti be recessed 7 to 9 mm. as the initial procedure in all cases of divergence excess, regardless of the amount of exodeviation, since esotropia is not to be feared.[178] I admit my delight with lateral rectus recessions, but I have respect for the fear of postoperative esotropia, despite my self-imposed rule of never recessing more than 7 mm. Lateral rectus recession is chosen over medial rectus resection if the near convergence is good.[163] Cases with near measurements of less than 25△ attain good surgical results.[178] The near measurement was found to be more than 10△ less than the distant exodeviation in 87% of exotropic children.[126] To weaken the lateral recti in the face of less exotropia at near should theoretically result in even a greater difference between distance and near measurements, since the medial recti would be relatively more unopposed when responding to the near vision reflex. However, 90% of 111 exotropes whose lateral recti were recessed experienced a diminution of difference between distance and near measurements. The explanation offered is that the accommodative convergence reflex had been adapted to compensate for the divergent misalignment so that even a slight accommodation evoked an exaggerated accommodative convergence, thus aiding binocularity. Eliminating the divergent misalignment by surgery removes the need for the adapted abnormal accommodation-accommodative convergence ratio, and within a few days to weeks it reverts back to normal in most instances.

Horizontal Noncomitant Strabismus

A 20-year study of 604 cases of extraocular muscle paralysis in Bologna revealed that 41% were sixth nerve, 33% were third nerve, and 5% were fourth nerve involvements.[179] Up to 20 years of age the etiology is chiefly encephalopathy followed by toxic infections and congenital paralysis; between 20 to 50 years of age it is trauma, and after 50 years of age vascular lesions and tumors cause most of the paralysis. A patient with benign rubella is described as developing total ophthalmoplegia followed by complete recovery.[180] Herpes zoster ophthalmicus caused seven cases of third nerve paralysis, followed by recovery.[181] There is conjecture about the cause being meningitis, semilunar ganglion invasion, or the result of an associated periarteritis nodosa. Chronic progressive ophthalmoplegia is discussed as being a sequela of encephalitis,[182] but earlier in this review the evidence of electromyography was cited that places this disorder under the classification of muscular dystrophy [16,24,25] (see Basic Science, Motor). An interesting case report relates chronic progressive ophthalmoplegia and retinitis pigmentosa.[183]

The types of ophthalmoplegia produced by disseminated sclerosis can be infranuclear, nuclear, internuclear, and supranuclear.[184] Nystagmus was found in 63% of 91 cases of extraocular muscle palsy caused by disseminated sclerosis. Thyroid dysfunction of the thyrotoxic type is associated with reduced tone of the voluntary musculature, eye muscles included, due to excessive thyroxin.[184] In advanced stages the fat content of extraocular muscles increases, causing severer weakness and, occasionally, permanent paresis. Thyrotropic exophthalmos, which was referred to previously as dysthyroid ophthalmople-

gia [25] (Basic Science, Motor), is produced by widespread changes in the orbital tissues, including the extraocular muscles, in which there occurs an increase in water and mucin content, fibrosis, and lymphocytic infiltration. The fibrotic changes are late secondary findings possibly due to prolonged venous congestion.

Since the contraction of a muscle is accompanied by relaxation of its antagonist, stimulation of its yoke, and inhibition of the antagonist of the yoke, a paralysis of one muscle modifies the function of the other three.[185] In fact, although tone is lost in the paralyzed muscle, the fibers do not become stretched and upon recovery they are as effective as ever.[114] But changes do take place in the antagonist muscle collagenous tissue and in the fascia surrounding the antagonist. The changes start early and ultimately interfere with movement of the eye, at which time the paralyzed muscle begins to recover. If fixation is with the paretic eye, such changes will not occur in the antagonist; rather, they will develop in the intermuscular septa and surrounding fascia of the contralateral synergist.

Two cases of unilateral exotropia with the involved eye manifesting a fibrotic lateral rectus and attenuated medial rectus, retraction of the globe on attempted abduction, and bulging on attempted adduction, plus homolateral ptosis, are presented.[186]

The bilateral Hummelscheim procedure as redescribed [187] provided a case of traumatic bilateral sixth nerve paralysis with binocularity and abduction.[188]

It is advised that extraocular muscle paralysis be treated with insufflation of air into the cerebrospinal system.[189]

A routine of physical therapy treatments daily for traumatic incurred ocular palsies is outlined.[190] Application of short-wave diathermy (electrodes applied to each side of the head) causes blood absorption, and iodide ionization (pad soaked in potassium iodide applied to the eye beneath a negative electrode) breaks down the fibrous tissue.

Vertical Strabismus

A vertical component occurs in 43% of cases of strabismus (242 of 566 cases).[191] Hyperfunction of the inferior obliques accounts for 74% (60% unilateral and 14% bilateral). Among 27 unrelated patients with hypertropia, 10 had relatives with the same condition and 3 had relatives with hyperphoria.[192] The inferior oblique involvement was of the vertical factor in 90% of the cases. In alternating horizontal strabismus with hyperfunction of the inferior obliques it is advised that one determine the hyperfunction separately with each eye fixating.[193]

Inferior oblique paralysis was encountered in 3.6% of 1047 cases,[194] 29 of 63 cases,[191] and 5 of 76 cases [108] of vertical muscle paralysis. A series of 97 cases [194] of inferior oblique palsy revealed that 21 were acquired, 70 were congenital, and 6 were of undetermined origin. Of the acquired group 6 were traumatic and 15 were operative complications (6 from accidental severance during lateral rectus surgery). Of the congenital group 16 had an associated ipsilateral superior rectus weakness while the remaining 54 had isolated inferior oblique weakness. Among the cases of congenital paralysis there was generally no overaction of the ipsilateral antagonist. In acquired cases the deficient secondary abduction action of the weak inferior oblique allows the eye to converge in straight-up gaze and diverge in down gaze owing to overaction of the superior oblique. This pattern was less prominent in unilateral palsies than in bilateral ones. Some cases of congenital origin demonstrated it. This could be used as evidence to substantiate that V-type exotropia is caused by an imbalance between inferior and superior obliques (see Basic Science, Motor, and Divergent Strabismus).

Inferior oblique weakness has also been suggested as the primary difficulty in superior oblique tendon sheath syndrome; yet electromyography has disproven this contention in some cases [25] (see Basic Science,

Motor). Since removal of the sheath of the superior oblique may not be durable treatment, because of its tendency to regrow,[195] tightening the ipsilateral inferior oblique is suggested in addition.[194,195]

Hypofunction of the superior rectus was found in 17 of 63 cases [191] and in 41 of 80 cases [108] in two different series of vertical muscle paralysis, whereas hypofunction of the superior oblique was encountered in 17 of the 63 cases [191] and 27 of the 80 cases.[108]

Torticollis is an adjunct to diagnosis of cyclovertical muscle palsy, but it is not a substitute for other more specific diagnostic methods.[196] The summarization is made that ocular torticollis does not fit into stereotyped patterns, although good reason exists for each particular head position. Head tilt is suggested to be rare in inferior oblique palsy but common in superior oblique and superior rectus weakness.[194] Surgery corrected the compensatory head position in 29 of 30 cases.[108] The contralateral inferior oblique was weakened in 13 cases of torticollis caused by superior rectus palsy (3 were bilateral), with excellent results in all.[197] Weakening of the ipsilateral inferior oblique was performed in 17 patients whose torticollis was due to superior oblique palsy (3 were bilateral), with good results in 11.

Blowout fracture of the floor of the orbit impounds orbital fat, inferior rectus, and oblique musculature.[198] Since the inferior rectus muscle tissue herniated and incarcerated into the fracture is nearer its insertion than the oblique, the movement effected by the inferior rectus is more limited than that produced by the inferior oblique. After 10 days irreversible degeneration and fixation of tissue sets in, reducing chances of full surgical restoration of function.

An anomalous insertion of the superior oblique tendon to the superior pole of insertion of the medial rectus is reported.[199] The misplaced insertion was transplanted to its normal site.

Supraclinoid carotid aneurysms were found in 8 of 11 cases with third nerve palsy.[200]

Diagnostic tests for vertical tropia are objective and subjective.[201,202] The simplest objective test is the Krimsky corneal reflex.[201] The secondary motor disturbance of contracture of the ipsilateral antagonist or contralateral synergist plus secondary sensory disturbances of amblyopia and abnormal retinal correspondence create diagnostic pitfalls.[202] Torticollis can be misleading.[202] Torsional deviations should also be studied.[201]

There is no substitute for surgery in treating vertical strabismus, but a depressor muscle should not be unduly weakened, since the lower fields are more important that the upper ones.[201]

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Correspondence

To the Editor:—Recently it was brought to my attention by one of our local social agencies that few practicing ophthalmologists are conversant with the proper handling of the person with a permanent visual handicap. The agency further pointed out that few medical schools have this important phase of patient management in their curricula. Although our educational programs undoubtedly are doing a better job of training men in the science of diseases of the eye, they evidently have been remiss in teaching the art of handling the patient whom medical science cannot help.

What usually happens, apparently, is that the average ophthalmologist simply announces to the patient or to his family, upon completion of the examination, that the patient's sight is beyond the help of medicine. The patient and his family are left to their own resources to find out what can be done to rehabilitate the patient to a useful life.

The social agency made the following suggestion, and I think it is an excellent one.

All ophthalmologists should acquaint themselves with the facilities available in their states to help reeducate and train the visually handicapped patient in skills that come within his potential.

Ophthalmologists also should equip themselves with the names and addresses of the various agencies that assist in the rehabilitation of the permanently visually handicapped person.

In other words, a positive approach to a permanent visual handicap would be better than the commoner negative attitude. Instead of simply announcing to the patient that he is beyond any help, it would be better to tell him that we can offer no medical help but that we suggest he consult ————————. At the same time, the patient would be given the names and addresses of the various agencies that have as their purpose the rehabilitation of the visually handicapped.

This simple procedure not only would soften the blow the patient feels when he learns he can expect no help from medicine but also would give him a ray of hope that he can learn to lead a productive life and escape being a burden to society or family.

William B. Clark, M.D.

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COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Harold G. Scheie, M.D., Chairman
William E. Krewson, 3rd, M.D., Clerk
Jan. 16, 1958

The Nervous Control of Intraocular Pressure. E. S. PERKINS, F.R.C.S., London, England.

The necessity of some control of the intraocular pressure and the mechanisms whereby such control can be exercised strongly suggest that the nervous system is involved. By analogy with other pressure systems in the body, it would be expected that the controlling nervous pathways would consist of pressure receptors in the eye, a sensory pathway, a central area in the brain, and an efferent pathway.

A team of workers under the direction of Sir Stewart Duke-Elder has been investigating the evidence for such a controlling mechanism, and, although it must be emphasized that to demonstrate that any particular nerve when blocked or stimulated causes changes in intraocular pressure does not prove that such a nerve is involved in the control of intraocular pressure, it has now been shown, at least in experimental animals, that nervous pathways do exist which could fulfill this function.

The sympathetic supply to the eye and the third, fifth, and seventh cranial nerves have all been studied, and the sympathetic system and fifth cranial nerve have been shown to exert definite effects on the intraocular pressure. Stimulation of certain areas of the diencephalon may also result in changes in intraocular pressure, and so efferent and central pathways probably exist. Little attention has been paid to the efferent or sensory pathways until recently, but it has now been shown that changes in the intraocular pressure in cats do provoke potentials in the long ciliary nerves which can be amplified and recorded, suggesting that there may be pressure-sensitive receptors in the eye. If this finding can be substantiated, there will be good evidence that the requisite pathways for a nervous control of intraocular pressure do exist, although the presence of such a control under normal conditions has not yet been proved.

News and Comment

ANNOUNCEMENTS

Ophthalmology Research Fellowship.—An annual research fellowship has been established for the Department of Ophthalmology of The Washington Hospital Center, Washington, D. C. (formerly The Episcopal Eye, Ear and Throat Hospital). Studies will include clinical work in the corneal clinic, keratoplasty, and animal experimentation. Stipend of $4800 per year, without meals or maintenance. Requirements, at least two years' residency in ophthalmology. Application forms may be obtained by writing to the Chairman, Ocular Research Committee, Washington Hospital Center, Washington 1, D. C.

Course in Eye Pathology.—The Department of Ophthalmology, Washington University School of Medicine, announces a one-week course in eye pathology, to be given by Dr. Theodore E. Sanders. The course will begin on July 28, 1958. For further information write the Department of Ophthalmology, Washington University School of Medicine, 640 S. Kingshighway, St. Louis 10.

Training for Orthoptic Technicians.—The Ohio State University, Department of Ophthalmology, offers a course for the training of orthoptic technicians. Any woman over 20 years of age who has successfully completed two years of college is qualified to apply. Graduate nurses are especially welcome. Candidates must enjoy working with children and meeting the general public.

The course consists of 12 months of didactic and practical training. We are confident that, as didactic lectures are given throughout the year, going hand-in-hand with practical training, this is one of the most comprehensive courses being given in this country. Lectures on refraction, optics, perimetry, general and ocular physiology, anatomy of the brain and orbit, and motility are given by members of the staff and the Ohio State University Medical School. The orthoptic training is conducted by two orthoptists, and students divide their time between the University Hospital Orthoptic clinic and that at Children's Hospital.

The course starts in September, and students are eligible to take the Board examinations for certification given by the American Orthoptic Council.

Limited financial assistance may be obtained from the Delta Gamma Sorority with headquarters in Columbus, Ohio.

For further information write to William H. Havener, M.D., Acting Chairman, University Hospital, The Ohio State University, Columbus 10, Ohio.

Home Study Courses.—The 1958-1959 Home Study Courses in the basic sciences related to ophthalmology and otolaryngology, offered as a part of the educational program of the American Academy of Ophthalmology and Otolaryngology, will begin on Sept. 1 and continue for a period of ten months. Detailed information and application forms may be secured from Dr. William L. Benedict, the executive secretary-treasurer of the Academy, 15 2d St. S. W., Rochester, Minn. Registrations should be completed before Aug. 15.

Postgraduate Courses for Specialists.—The Institute of Ophthalmology of the Americas of the New York Eye and Ear Infirmary announces a series of postgraduate courses for specialists to be given from Nov. 3, 1958, to Jan. 9, 1959.

Courses will be given in the following subjects: Anomalies of Extraocular Muscles, including Ptosis; Aniseikonia; Biomicroscopy; Cataracts; Clinical Bacteriology; Complications of Ophthalmic Surgery; Electrophysiology of the Eye; Glaucoma; Gonioscopy and Tonography; Keratectomy and Keratoplasty; Lacrimal Sac Surgery; Medical Ophthalmoscopy; Near Ultra-Violet Biomicroscopy; Ocular Allergy; Ocular Biochemistry; Ocular Microbiology; Ocular Neuro-Ophthalmology; Ocular Photography; Ocular Radiology; Ocular Trauma; Ophthal-

moscopy; Pathology; Perimetry; Plastic Eye Surgery; Pleoptics and Macular Function Testing; Psychosomatic Factors in Ophthalmology; Radio-Isotopes in Ophthalmology; Refraction, and Retinal Detachment.

Further information regarding the courses may be obtained by writing to Mrs. Tamar Weber, Registrar, Institute of Ophthalmology of the Americas of the New York Eye and Ear Infirmary, 218 2d Ave. New York 3.

GENERAL NEWS

The Friedenwald Lectureship.—The Friedenwald Lectureship has been established under the auspices of the Association for Research in Ophthalmology as a memorial to Dr. Jonas S. Friedenwald. The first such lecture was given by Dr. John E. Harris at the 1957 meeting of the Association. Recently it has been announced that Dr. Bernard Becker will give the Friedenwald Lecture for 1958. It is apparent that the Friedenwald Lecture will become the highlight of the annual session of the Association for Research in Ophthalmology.

Almost immediately after the death of Dr. Friedenwald the Trustees of the Association for Research in Ophthalmology appointed an ad hoc committee to plan a suitable memorial for Dr. Friedenwald. A number of different means of honoring Dr. Friedenwald's memory were considered. The Committee thought, considering Dr. Friedenwald's interests and ideals, that an award to encourage and recognize research activity by young investigators would best perpetuate his memory. Rather than serving the function of an additional award for established investigators, as does the Proctor Medal of the Association, emphasis will be placed on those who have received less recognition and whose contributions are current. Recipients will be invited to present a lecture on any phase of ophthalmic research at the annual meeting of the Association. A stipend of $500.00 will be awarded to the recipient.

Almost immediately after the appointment of the Committee a number of Dr. Friedenwald's friends and associates sent contributions to start a Friedenwald Memorial Fund under the auspices of the same Committee. The family of Dr. Friedenwald also contributed most generously to the fund. At no time has there been a public request for contributions. This fund has now been turned over to the Trustees of the Association for Research in Ophthalmology as a permanent endowment fund for the Friedenwald Lectureship. Further contributions to the fund are necessary if it is to adequately carry out this function. All those interested in perpetuating the memory of a great ophthalmologist whose contributions are so important to all ophthalmologists are invited and urged to send contributions to this fund. They may be sent to the Secretary of the Association for Research in Ophthalmology, Dr. Lorand V. Johnson, 10515 Carnegie Ave., Cleveland.

Suggestions for possible candidates for the awards would be welcomed by the Trustees. These may also be sent to Dr. Johnson.

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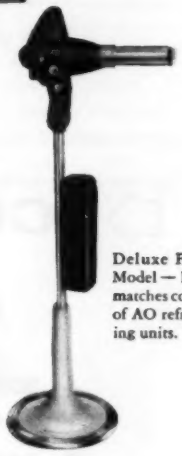
Table Model No. 1217-A Project-O-Chart

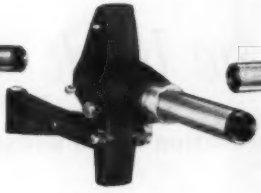
Wide Selection of Models

Standard Floor Model — Black wrinkle finish.



Deluxe Floor Model — Base matches colors of AO refracting units.

Wall Model—Use when floor space is at a premium.



Unit Model—Mounts by bracket on refracting unit.

Portable Model—Same as table model with screen and carrying case.

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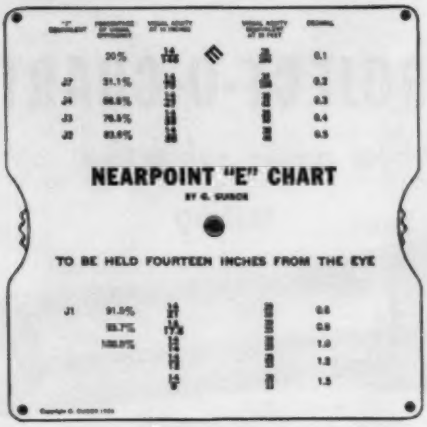

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E-83*	Cataract Knife, VON GRAEFE: 30mm x 2mm.	
E-84*	Cataract Knife, VON GRAEFE: 33mm x 2.3mm.	
E-85*	Cataract Knife, VON GRAEFE: 35mm x 2.5mm.	
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*Designates STAINLESS STEEL.

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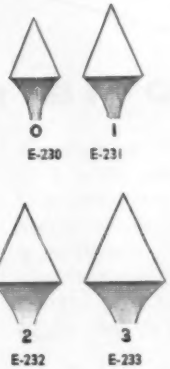

E-230 E-231 E-232 E-233

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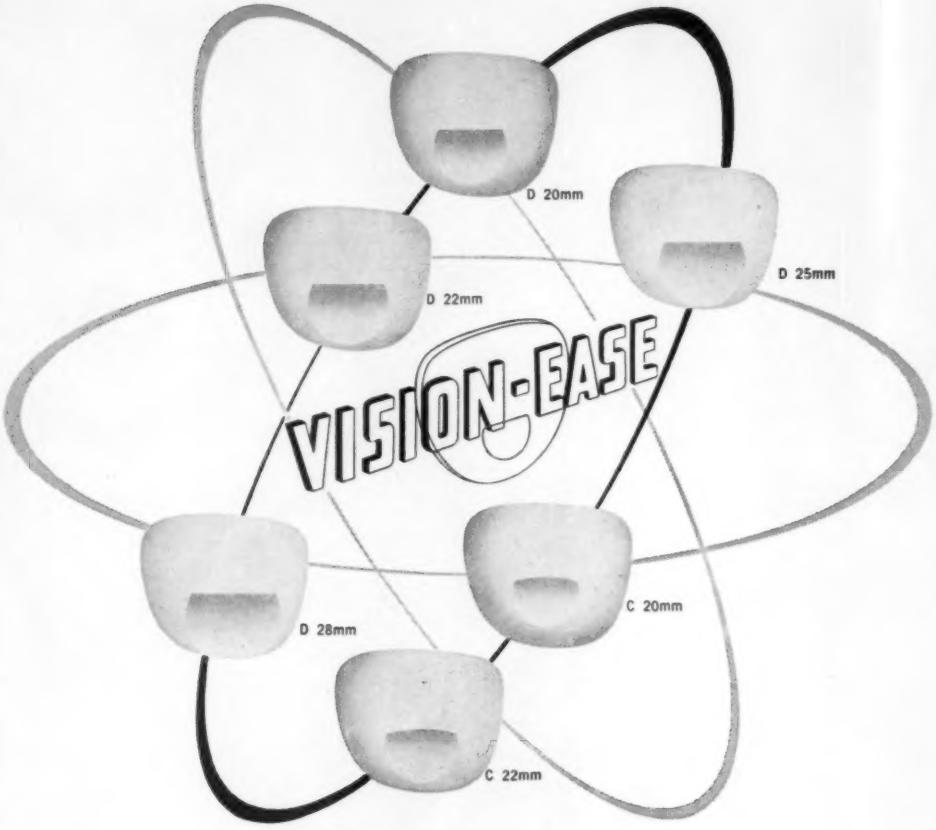

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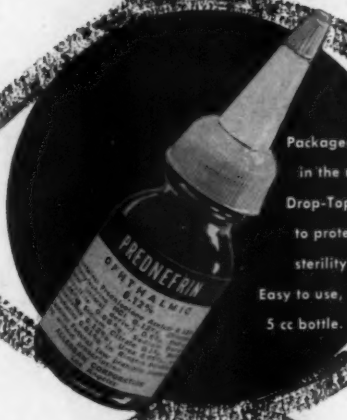

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